Lanthanides: Chemistry and Use in Organic Synthesis

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Lanthanides: Chemistry and Use in Organic Synthesis

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The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry, where new developments are having a significant influence on such diverse areas as organic synthesis, pharmaceutical research, biology, polymer research and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry. Coverage is designed for a broad academic and industrial scientific readership starting at the graduate level, who want to be informed about new developments of progress and trends in this increasingly interdisciplinary field. Where appropriate, theoretical and mechanistic aspects are included in order to help the reader understand the underlying principles involved.
The individual volumes are thematic and the contributions are invited by the volumes editors.
In references Topics in Organometallic Chemistry is abbreviated
Top. Organomet. Chem. and is cited as a journal

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Preface

While the lanthanides (strictly defined as the 14 elements following lanthanum in the periodic table, but as normally used also include lanthanum itself) have several unique characteristics compared to other elements, their appearance in the history of the development of organometallic chemistry is rather recent. Since the f orbitals are filled gradually from lanthanum ($[Xe]4f^0$) to lutetium ($[Xe]4f^{14}$), they are regarded as the f-block elements, which are discriminated from the d-block transition elements.

This book was edited as the second volume of "Topics in Organometallic Chemistry", aiming at an overview of recent advances of chemistry and organic synthesis of lanthanides. Since scandium (Sc) and yttrium (Y) (which lie above the lanthanides and have similar characteristics) are also included, this book covers rare earth chemistry. Recently, especially in this decade, the chemistry and organic synthesis of lanthanides have developed rapidly as one of the most exciting areas. An international team of authors has been brought together in order to provide a timely and concise review of current research efforts such as lanthanide catalysis in small molecule organic synthesis especially focused on carbon-carbon bond-forming reactions, chemistry and organic synthesis using low-valent lanthanides such as diiodosamarium, asymmetric catalysis, lanthanide-catalyzed polymer synthesis, and polymer-supported lanthanide catalysts used in organic synthesis. Principles of organolanthanide chemistry are summarized in the first chapter. I am sincerely grateful to Drs. R. Anwander, E. C. Dowdy, H. Gröger, Z. Hou, H. Kagan, G. Molander, J. L. Namy, M. Shibasaki, Y. Wakatsuki, and H. Yasuda for participating in this volume. J. Richmond, J. Sterritt-Brunner, and B. Benner (Springer) are also acknowledged for encouraging me to organize this work.

Finally, I hope that this volume is helpful to many researchers and students who are or will be involved in or interested in this truly exciting and hot field.

Tokyo, December 1998   Shū Kobayashi

Contents

Principles in Organolanthanide Chemistry

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During the last decade, the rare earth elements have given enormous stimulus to the field of organic synthesis including stereoselective catalysis. This article outlines both the basic and advanced principles of their organometallic chemistry. The intrinsic electronic features of this 17-element series are reviewed in order to better understand the structural chemistry of their complexes and the resulting structure–activity relationships. Particular emphasis is placed on synthetic aspects, i.e. optimization of established procedures and alternative methods with better access to catalytically relevant species. Accordingly, tailor-made ancillary ligands are reported in detail and the reactivity pattern of lanthanide compounds is examined with representative examples.

Keywords: Lanthanides, Intrinsic properties, Reactivity, Synthesis, Ligands

List of Abbreviations

Ar   aromatic residue
BINOL   binaphthol
CN   coordination number
COT   cyclooctatetraenyl
Cp η^5-cyclopentadienyl
Cp* η^5-pentamethylcyclopentadienyl
DME   1,2-dimethoxyethane
HMPA   hexamethylphosphoric triamide
HSAB   hard soft acid base
L   ligand
Ln   lanthanide (Sc, Y, La, Ce-Lu)
MMA   methylmethacrylate
OTf   trifluoromethanesulfonato ("triflate"), CF_3SO_3
Ph   phenyl
PMDETA   N, N, N',N",N"-pentamethyldiethylenetriamine
Py   pyridine
R   residue
salen   *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)ethylenediamine
Tp   tris(pyrazolyl)borate
THF   tetrahydrofuran
TMEDA   tetramethylethylenediamine
X   ligand
Z   nuclear charge

1
Introduction

The rare earth elements constitute an integral part of modern organic synthesis [1]. It was about 30 years ago that the peculiar redox behavior of several inorganic reagents was discovered for selective reductive and oxidative conversions [2]. In the interim period fine chemicals and polymer synthesis have increasingly benefited from the application of highly efficient organolanthanide precatalysts [3]. Due to their intrinsic electronic properties expressed in the "lanthanide contraction", the rare earth elements comprising the group 3 metals Sc, Y, La and the inner transition metals Ce-Lu provide new structural and reactivity patterns, emerging in structure-activity relationships unprecedented in main group and d-transition metal chemistry. It is also their low toxicity and availability at a moderate price which makes this "17-element series" attractive for organic synthesis. The spectrum of rare earth reagents ranges from inorganic to organometallic compounds as schematically redrawn in Fig. 1 with representative examples.

While highly efficient inorganic reagents such as $SmI_2(thf)_2$ and $Sc(OTf)_3$ are already commercially available, the more sophisticated organometallic reagents are as a rule prepared on a laboratory scale, often under rigorous exclusion of moisture using inert gas techniques [4]. In particular, the latter class of compounds offers access to tailor-made, well-defined molecular species via ligand fine-tuning. The consideration of the intrinsic properties of the lanthanide cati-
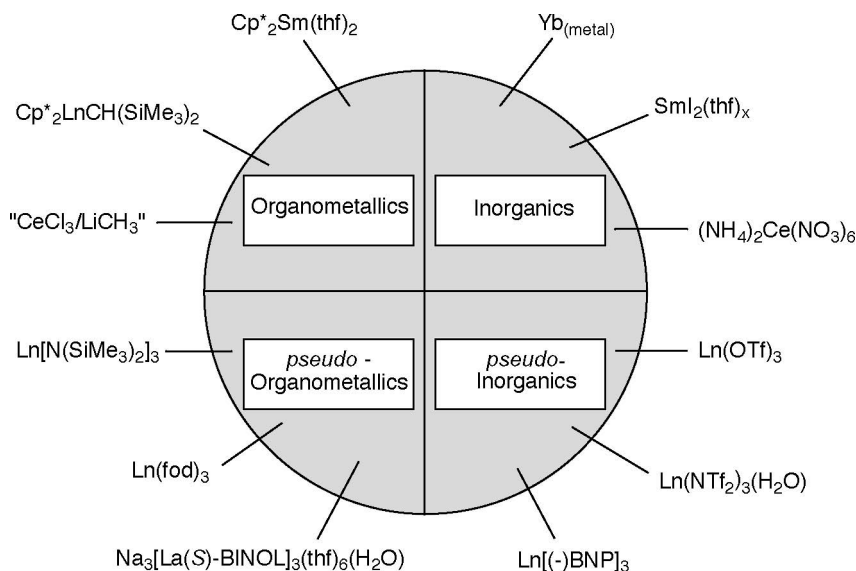
Fig. 1. Rare earth metal reagents in organic synthesis (NTf₂=bis[trifluoromethyl)sulfonyl]amide, (–)BNP=(R)-(–)-1,1'-binaphthyl-2,2'-diylphosphato)

ons as well as thermodynamic and kinetic factors are crucial in designing and synthesizing novel molecular compounds. This article also includes reference to highly reactive metalorganic compounds, *pseudo-organometallics*, containing no direct metal carbon linkage; containing, however, otherwise readily hydrolyzable Ln-X bonds. For example, lanthanide compounds such as amide and alkoxide derivatives not only display important synthetic precursors but also exhibit excellent catalytic behavior in organic transformations [5,6]. Macrocyclic ligands exhibiting Ln–N and Ln–O bonds are not considered in this survey [7]. The last 20 years have witnessed a rapid development in organolanthanide chemistry and numerous review articles have been published, emphasizing various aspects including their use in organic transformations. A comprehensive list of relevant articles has been given recently [8]. The purpose of this article is not to give a comprehensive survey of organolanthanide compounds but rather to address the principles of their chemistry.

2
Intrinsic Properties of the Lanthanide Elements

The rare earth elements represent the largest subgroup in the periodic table and offer a unique, gradual variation of those properties which provide the driving force for various catalytic processes. Their peculiar electronic configuration and the concomitant unique physicochemical properties also have to be consulted for the purpose of synthetic considerations. The highly electropositive character of the lanthanide metals, which is comparable to that of the alkali and alkaline earth metals, leads as a rule to the formation of predominantly *ionic* compounds, Ln(III) being the most stable *oxidation state* [9]. This and other intrinsic properties are outlined in Scheme 1 which will serve as a point of reference in this section [10–13].

2.1
Electronic Features

The Ln(III) cations of the series Ce–Lu exhibit the extended Xe-core electronic configuration $[Xe]4f^n$ (n=1–14), a symbol which perfectly pictures the limited radial extension of the f-orbitals: The $4f$ shell is embedded in the interior of the ion, well-shielded by the $5s^2$ and $5p^6$ orbitals [14]. A plot of the radial charge densities for the $4f$, $5s$, $5p$ and $6s$ electrons for Gd^+ visually explains why Ln(III) cations are commonly thought of as a *"triple-positively charged closed shell inert gas electron cloud"* (Fig. 2) [14].

Ionization energies of the elements [15], optical properties [16], and magnetic moments of numerous complexes [17] prove that the f-orbitals are perfectly shielded from ligand effects. Consequently, only minimal perturbation of the f-electronic transitions results from the complexation of dipolar molecules. In contrast to the broad $d{\rightarrow}d$ absorption bands of the outer transition elements, the $f{\rightarrow}f$ bands of the lanthanides are almost as narrow in solid and in solution as

Ln^{4+} [E^0 (M^{4+}/M^{3+}), V] →   1.74 3.2   3.1

Ln^{3+} [10]   →   Sc Y La ‖ Ce Pr Nd Pm Sm Eu Gd ‖ Tb Dy Ho Er Tm Yb Lu

Ln^{2+} [E^0 (M^{2+}/M^{3+}), V] →   -1.55 -0.36   -2.1 -1.15

Cation Size (Å) [11]   0.745 1.032 1.01 _____ 0.938 _____ 0.861
(Ln^{3+}, 6-coordination)

Electronic Configuration   [Ar] [Kr] [Xe] [Xe]4f^1——————————[Xe]4f^{14}
(Ln^{3+})

Lewis Acidity
(Ln^{3+}, relative)

Oxophilicity [12]   165 170 190 188 [167 — 136 112 170 [_____] 144 122 95 159
[D$_0$(LnO), (± 5 kcalmol^{-1})]

Electronegativity [13]   1.3 1.2 1.1 1.1 ——————————————— 1.1
(Pauling)
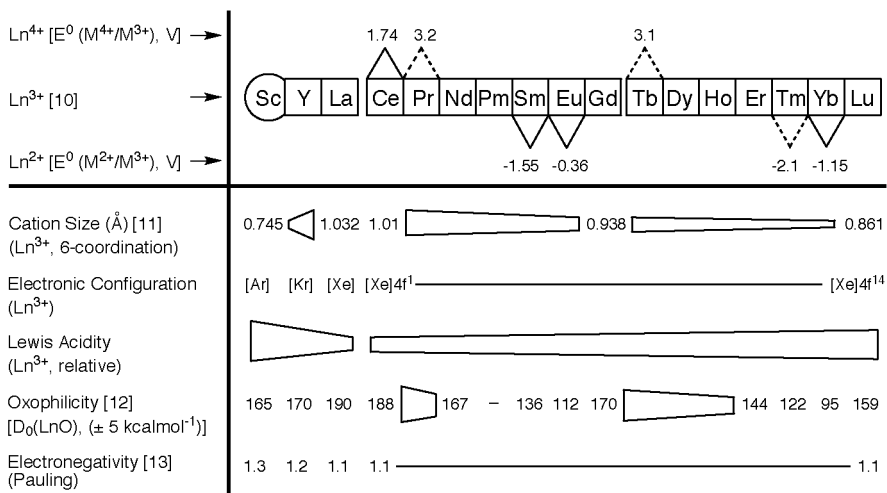
Scheme 1. Trends within intrinsic properties of the lanthanide elements

Fig. 2. Plot of the radial charge densities for the 4f-, 5s-, 5p-, and 6s-electrons of Gd$^+$ from [14]

they are for gaseous ions. These transitions are "LaPorte-forbidden" and result in weak intensities which are responsible for the pale color of the trivalent species. General principles of *d*-transiton metal ligand bonding such as σ-donor/π-acceptor interaction, the "18-electron rule", and the formation of classic carbene, carbyne, or carbon monoxide complexes are not observed in lanthanide chemistry, neither do they form Ln=O or Ln≡N multiple bonds. However, the lack of orbital restrictions, e.g. the necessity to maximize orbital overlap as in *d*-transition metal chemistry, allows "orbitally forbidden" reactions. Because of very small crystal-field splitting and very large spin-orbit coupling (high Z) the energy states of the $4f^n$ electronic configurations are usually approximated by the Russel–Saunders coupling scheme [18]. The peculiar electronic properties of the *f*-elements have proved attractive for numerous intriguing opto- and magneto-chemical applications ("probes in life") [15].

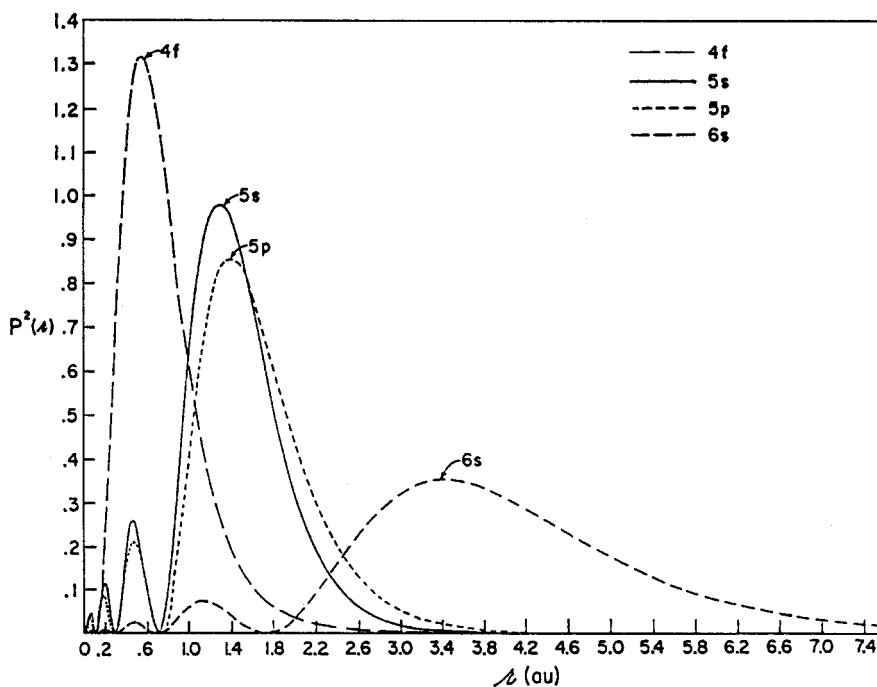The inert gas-core electronic configuration also implies a *conform chemical behavior* of all of the Ln(III) derivatives including Sc(III), Y(III) and La(III). The contracted nature of the 4*f*-orbitals and concomitant poor overlap with the ligand orbitals contribute to the predominantly ionic character of organolanthanide complexes. The existing electrostatic metal ligand interactions are reflected in molecular structures of irregular geometry and varying coordination numbers. According to the HSAB terminology of Pearson [19], lanthanide cations are considered as *hard acids* being located between Sr(II) and Ti(IV). As a consequence, "hard ligands" such as alkoxides and amides, and also cyclopentadienyl ligands show almost constant effective ligand anion radii (alkoxide: 2.21±0.03 Å; amide: 1.46±0.02; cyclopentadienyl: 1.61±0.03) [20] and therefore fit the evaluation criteria of ionic compounds according to Eigenbroth and Raymond [21]. The ionic bonding contributions in combination with the high Lewis acidity cause the strong *oxophilicity* of the lanthanide cations which can be expressed in terms of the dissociation energy of LnO [12]. The interaction of the oxophilic metal center with substrate molecules is often an important factor in governing chemo-, regio- and stereoselectivities in organolanthanide-catalyzed transformations [22]. Complexation of the "softer" phosphorus and sulfur counterions is applied to detect extended covalency in these molecular systems [23,24].

Scheme 1 further indicates the tendency of the Ln(III) cations to form the more unusual oxidation states in solution [25]. Hitherto, organometallic compounds of Ce(IV), Eu(II), Yb(II) and Sm(II) have been described in detail [4]. More sophisticated synthetic approaches involving metal vapor co-condensation give access to lower oxidation states of other lanthanide elements [26]. Charge dependent properties such as cation radii and Lewis acidity significantly differ from those of the trivalent species. Ln(II) and Ce(IV) ions show very intense and ligand-dependent colors attributable to "LaPorte-allowed" 4*f*→5*d* transitions [16b]. Complexes of Ce(IV) and Sm(II) have achieved considerable importance in organic synthesis due to their strongly oxidizing and reducing behavior, respectively [1,27]. Catalytic amounts of compounds containing the "hot oxidation states" also initiate substrate transformations. As a rule this implies a switch to the more stable, catalytically acting Ln(III) species [28].

2.2
Steric Features

Structural changes in homologous rare earth compounds arise from the *lantha-nide contraction* [29], i.e. the monotonically decreasing ionic radii with increasing atomic number. The 4*f*-electrons added along the lanthanide series from lanthanum to lutetium do not shield each other efficiently from the growing nuclear charge, resulting in the contraction phenomenon. It is often this varying cationic size which has a tremendous effect on the formation, coordination geometry (coordination numbers) and reactivity of their complexes. Reports have accumulated where organic substrates seem to discriminate not only between ligand environments but also between single lanthanide elements [22]. Successful explanations of these phenomena are based on the systematic theoretical investigation and structural characterization of organolanthanide compounds [4].

Scheme 1 gives the trend of ionic radii of these *"large" cations* which prefer formal coordination numbers in the range of 8–12 [30]. For example, considering the effective Ln(III) radii for 6-coordination, a discrepancy of 0.171 Å between Lu(III) and La(III) allows the steric fine-tuning of the metal center [11]. The structural implications of the lanthanide contraction are illustrated in Fig. 3 with the well-examined homoleptic cyclopentadienyl derivatives [31]. Three structure types are observed depending on the size of the central metal atom: **A**, $[(\eta^5\text{-Cp})_2\text{Ln}(\mu\text{-}\eta^5\text{:}\eta^x\text{-Cp})]_\infty$ $1\leq x\leq2$; **B**, $\text{Ln}(\eta^5\text{-Cp})_3$; **C**, $[(\eta^5\text{-Cp})_2\text{Ln}(\mu\text{-}\eta^1\text{:}\eta^1\text{-}$ Cp)]$_\infty$; these exhibit coordination numbers of 11 (10), 9, and 8, respectively. In
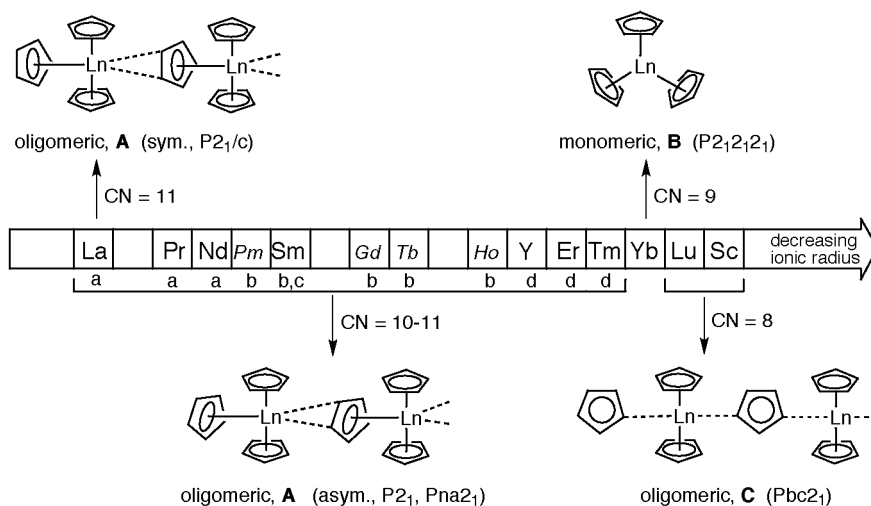

Fig. 3. Coordination modes in homoleptic, ionic LnCp$_3$ derivatives (*a* belong to space group P2$_1$; *b* indication from powder diffraction pattern; *c* show additional modifications Pbcm and P2$_1$/n (contact dimer – effect of crystallization conditions [31b]); *d* belong to space group Pna2$_1$ and exhibit lengthened intermolecular Ln-C contacts)

accord with ionic bonding, small changes in ligand substitution lead to changed coordination behavior and number (CN=10), as found in the tetranuclear ring structure of the "MeCp" derivative. Monomeric type **B** is preferentially formed with ligands bearing bulky substituents.

High coordination numbers can usually be accomplished in oligomeric structures or highly solvated complexes. However, both forms are undesirable for synthesizing highly reactive compounds. The reactivity and stability, respectively, of lanthanide complexes is correlated with the steric situation at the metal center. Evaluation criteria as the principle of "steric saturation/unsaturation/oversaturation" have been developed to explain the differences in reactivity [32]. Hence, the main synthetic efforts as in d-metalorganic chemistry are put into the fine-tuning of the ligand sphere to obtain tractable (volatile, catalytically reactive, etc.) compounds. Because of the importance of steric factors, ligand environments have been numerically registrated, e.g. by the "cone-packing model" [33], which represents a 3-D extension of *Tolman's* "cone-angle model" [34]. In this model, solid angles are calculated from structural data employing van der Waals radii [35] and considering effects of second order packing. The introduction of steric coordination numbers for various types of ligands based on solid angle ratios further emphasizes the importance of steric considerations in organo-*f*-element chemistry [36].

The *Lewis acidity* which is affected by the charge density (Z/r) is less distinct in complexes derived from the large Ln(III) cations. Hence, these systems are often reported as mild Lewis acidic catalysts in organic synthesis [1]. However, Sc(III) as by far the smallest Ln(III) cation is located in a "pole position" not only with respect to Lewis acidity. Its "aluminum/lanthanide/early transition metal hybrid character" [37] has revealed its superiority in many catalytic applications [37,38]. Based on their relative preferences for pyridine, Lappert suggested a relative Lewis acidity scale: $Cp_2ScMe>AlMe_3>Cp_2YMe\approx Cp_2LnMe$ (here: Ln=large lanthanide elements) [39]. Maximum electrostatic metal/ligand interaction and ionic bond strength (enhanced *complex stability*) is also expected for scandium, the smallest element. The Ln(III) charge density and the concomitant complexation tendency also prove useful when studying the nature of Ca^{2+} binding in biological macromolecules exploiting the lanthanide elements as spectroscopic and magnetic probes [15].

3
Synthesis of Organolanthanide Compounds

The availability of pure and well-defined starting materials is crucial for straightforward and high-yield syntheses of organometallic rare earth compounds. The suitability of both synthetic and catalyst precursors can be judged by the consideration of thermodynamic and kinetic factors. For example, the knowledge of metal–ligand bond strengths can assist in a better analysis of the thermodynamics of archetypical ligand exchange reactions and to elaborate the mechanistic scenarios of catalytic transformations [40].

3.1
Thermodynamic and Kinetic Guidelines

Marks and co-workers provided a most valuable examination of absolute bond disruption enthalpies of various relevant metalorganic ligands X in Cp^*_2Sm-X. The data were obtained by anionic titration calorimetry in toluene (Fig. 4) [41]. Although the Ln–X bonds seem to be thermodynamically very stable, they usually display kinetic lability due to high ligand exchange ability, chelating and solubility effects.

Scheme 2 encompasses important synthetic building blocks and preferred synthetic strategies in organolanthanide chemistry. As acid/base-type exchange reactions are fundamental, the ligands are depicted according to their increasing pK_a values (in water). This also correlates with the tendency to hydrolyze (organometallics) or with the competition between solvation and complexation on the basis of the HSAB concept (inorganics).

The central point in this consideration is the Ln–OH moiety, the preferred formation of which is called a "dilemma in organolanthanide chemistry". Organolanthanide and pseudo-organolanthanide compounds readily hydrolyze when exposed to air and moisture, with the formation of hydroxide and oxo-centered ligand cluster intermediates. Lanthanide complexes with Ln–C linkages are considered as "oversensitive" compounds [42]. Even ligands with lower pK_a values than water, as exemplified by substituted phenol ligands, tend to hydrolyze in organic solvents because the insoluble hydroxides formed act as a driving force. However, the presence of hard donor functionalities or multiply charged anions which are capable of chelation, can afford moisture-stable alkoxide and amide complexes, as has been shown for BINOL [43], polypyrazolylborate [44] and porphyrin-like complexes [45]. Nevertheless, all of the organolanthanide complexes should routinely be handled under an inert gas atmosphere by application of high vacuum and glove-box techniques [46].
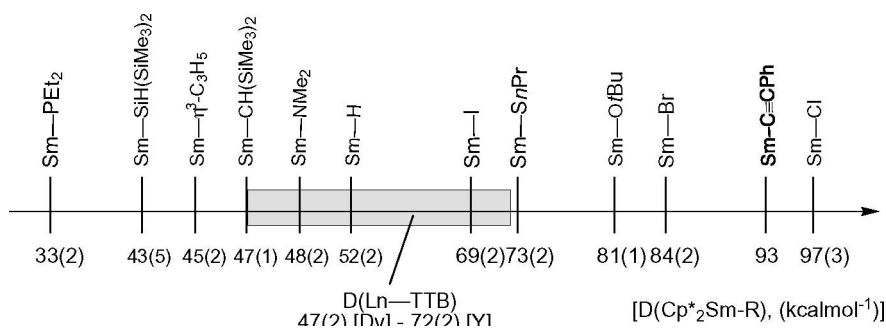
Fig. 4. Bond disruption enthalpies of organolanthanide(III) complexes. The *gray area* indicates the bond disruption enthalpies of organolanthanide(0) arene species (TTB=η^6-$C_6H_3tBu_3$-1,3,5)
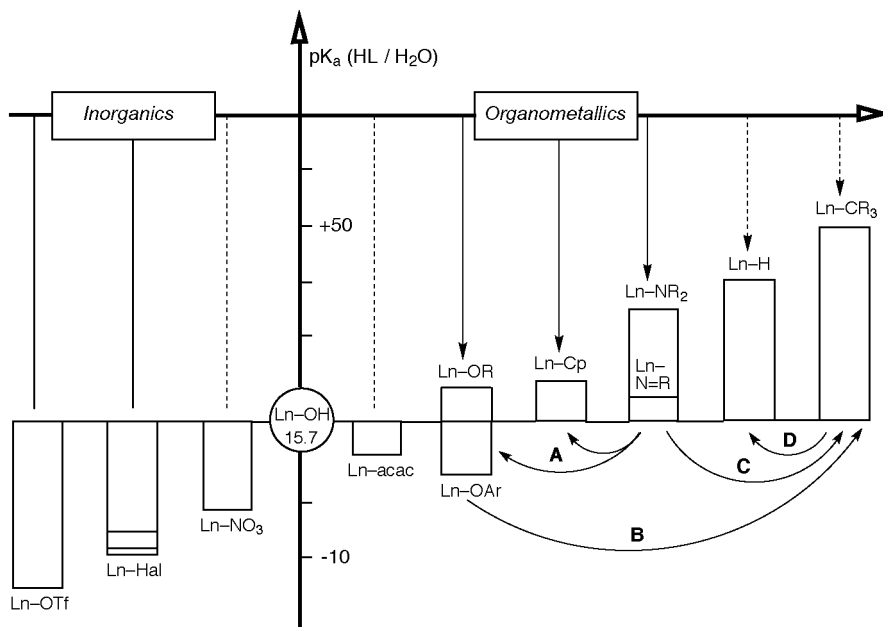
Scheme 2. Synthetic strategies towards organolanthanide compounds [**A:** amine elimination reactions, e.g. *silylamide route*; **B:** alkylation via alkoxide precursor, e.g. *aryloxide route*; **C:** alkylation via amide precursor; **D:** hydrogenolysis of alkyl moieties]

3.2
Inorganic Reagents

Lanthanide halides, nitrates and triflates are not only common reagents in organic synthesis (Fig. 1) but also represent, in dehydrated form, key precursor compounds for the more reactive organometallics (Scheme 2). As a rule, in compounds of strong monobasic acids or even superacids, cation solvation competes with anion complexation, which is revealed by fully or partially separated anions and solvated cations in their solid state structures. The tendency to form outer sphere complexation in coordinating solvents [47] is used as a criterion of the reactivity of inorganic salt precursors in organometallic transformations.

Ln-Halides
Anhydrous lanthanide halides are ionic substances with high melting points which take up water immediately when exposed to air to form hydrates ($I^- > Br^- > Cl^-$) [48]. Straightforward synthetic access and a favorable complexation/solvation behavior make the lanthanide halides the most common precursors in organolanthanide chemistry. Many important Ln–X bonds (X=C, Si, Ge, Sn, N, P, As, Sb, Bi, O, S, Se, Te) can be generated via simple salt metathesis reactions [4,8]. The so-called *ammonium chloride route* either starting from the lanthanide oxides or

$$LnCl_3(H_2O)_x \xrightarrow[\substack{\approx 150\ ^\circ C/10^{-4}\ torr,\ -H_2O \\ \approx 350\ ^\circ C/10^{-4}\ torr,\ -NH_4Cl}]{NH_4Cl} LnCl_3 \xrightarrow[soxhlet]{THF} LnCl_3(thf)_x$$

$x = 6,7$ → $x = 1.33\text{-}3.5$

$$\xrightarrow{\approx 150\ ^\circ C/10^{-2}\ torr,\ -H_2O} [CeCl_3(H_2O)]_n$$

$$\xrightarrow{> 350\ ^\circ C/10^{-2}\ torr,\ -H_2O} \text{"LnOX"}$$

$$Sc_2O_3 \xrightarrow{HCl(aq.)} ScCl_3(H_2O)_6 \xrightarrow[80\ ^\circ C]{\substack{SOCl_2,\ THF \\ -SO_2,\ -HCl}} ScCl_3(thf)_3$$
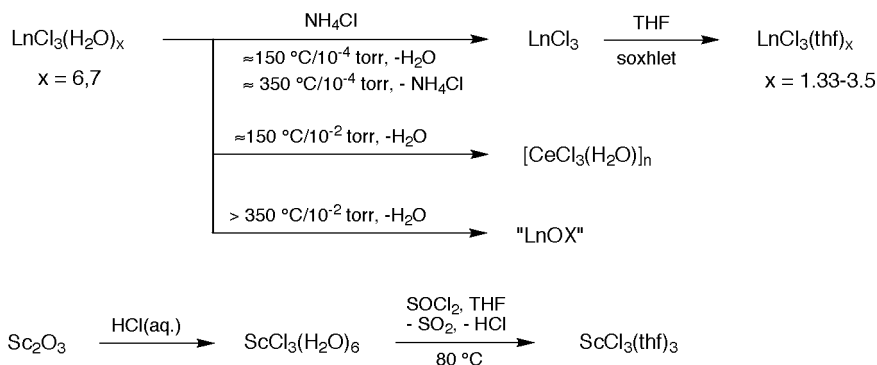
Scheme 3. Laboratory procedures for the preparation of lanthanide chloride precursors

the hydrated halides is the most popular laboratory procedure (upscaling is possible) to anhydrous lanthanide(III) chlorides (Scheme 3) [49]. Simple thermal dehydration which works well for lanthanide triflates leads to the formation of undesired lanthanide oxychlorides. Evans and co-workers have shown that the standard recipe for dehydrating $CeCl_3(H_2O)_7$ to make $CeCl_3/RLi$ will produce $[CeCl_3(H_2O)]_n$ [50]. "$CeCl_3/RLi$" is a popular Grignard-type reagent in organic synthesis [51] which, for example, increasingly tolerates functional groups.
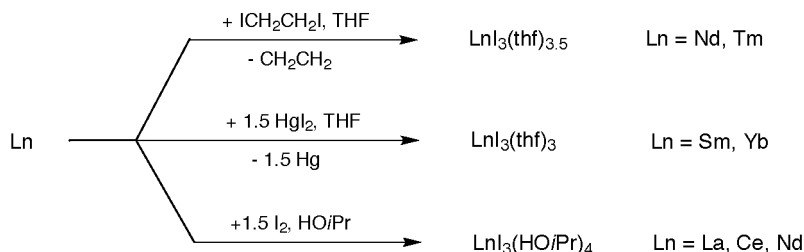
A coordinating solvent such as tetrahydrofuran (THF) is often necessary to react the otherwise insoluble lanthanide halides via salt metathesis. These reactions proceed via initial formation of the more soluble compounds $LnX_3(thf)_x$, which are obtained via Soxhlet extraction and are popular, well-defined starting reagents [52]. The extent of THF coordination depends on both the structural type of the anhydrous lanthanide halide and the prevailing crystallization conditions, and affects its solubility and hence its reactivity [53]. "$ScCl_3(thf)_3$" is best synthesized by an alternative procedure utilizing $SOCl_2$ as a dehydrating agent [54]. Neutral donor ligands such as caprolactone [53a], 2,6-dimethyl-4-pyrone [55] or chelating ligands such as DME [56] and crown ethers [57,58] also reveal unforeseen and intriguing coordination chemistry.

Other small-scale laboratory procedures have been developed for the direct synthesis of the more reactive THF adducts, avoiding "inconvenient" high temperature treatment [59–62]. For example, the preparation of "$LnCl_3(thf)_x$" from metal powder and hexachloroethane is facilitated by sonication [Eq. (1)] [59]. Additional metal-based synthetic routes include the redox transmetallation with mercury(II) halides [Eq. (2)] [60] and the reaction with trimethylsilyl chloride and anhydrous methanol [Eq. (3)] [61]. Ammonia has been employed as an alternative donating solvent in the synthesis of lanthanide alkoxides starting from lanthanide chlorides [63].

$$2\ Ln + C_2Cl_6 \xrightarrow[)))]{THF} 2\ LnCl_3(thf)_x + C_2Cl_4 \qquad (1)$$

$$\text{Ln} \begin{cases} \xrightarrow[\text{- CH}_2\text{CH}_2]{+ \text{ICH}_2\text{CH}_2\text{I, THF}} & \text{LnI}_3(\text{thf})_{3.5} \qquad \text{Ln = Nd, Tm} \\[2em] \xrightarrow[\text{- 1.5 Hg}]{+ 1.5 \text{ HgI}_2\text{, THF}} & \text{LnI}_3(\text{thf})_3 \qquad \text{Ln = Sm, Yb} \\[2em] \xrightarrow[]{+1.5\text{ I}_2\text{, HO}i\text{Pr}} & \text{LnI}_3(\text{HO}i\text{Pr})_4 \qquad \text{Ln = La, Ce, Nd} \end{cases}$$

Scheme 4. Small-scale synthesis of solvated Ln(III) iodides

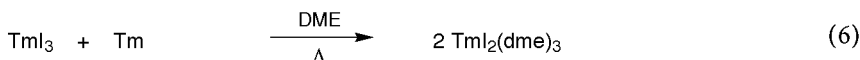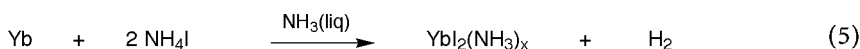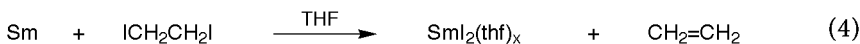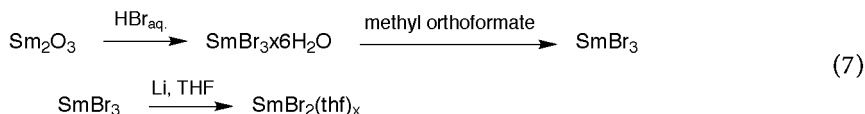$$2\text{ Ln} \; + \; 3\text{ HgCl}_2 \xrightarrow[\Delta]{\text{THF}} 2\text{ LnCl}_3(\text{thf})_x \; + \; 3\text{ Hg} \tag{2}$$

$$\text{Ln = Yb (x = 3); Er (x = 3.5); Sm (x = 2); Nd (x = 1.5)}$$

$$2\text{ Ln} \; + \; 6\text{ Me}_3\text{SiCl} \; + \; 6\text{ MeOH} \xrightarrow[\Delta]{\text{THF}} 2\text{ LnCl}_3(\text{thf})_x \; +$$
$$+ \; 6\text{ Me}_3\text{SiOMe} \; + \; 3\text{ H}_2 \tag{3}$$
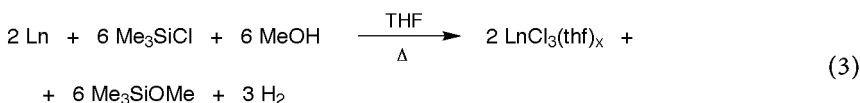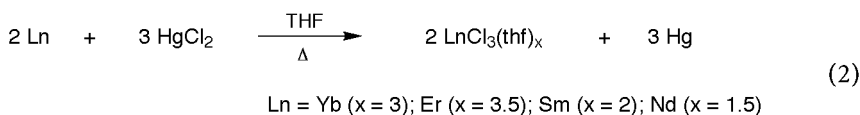
Scheme 4 shows small-scale syntheses of solvated iodides [64–66]. Strongly donating solvents such as *N*-methylimidazole (*N*-MeIm) can accomplish complete anion/cation separation as shown for $[\text{Sm}(N\text{-MeIm})_8]\text{I}_3$ under anaerobic conditions [67]. The chief factors which affect the often enhanced reactivity of the higher homologous halides are their higher solubility [48a], a thermodynamically more labile Ln–X bond (Fig. 4), the soft Lewis basicity of the iodide anion, and different solubility properties of the eliminated alkali metal salt.

Lanthanide(II) halides, in particular iodides, are prominent synthetic precursors to the corresponding Ln(II) organometallics [32,68,69]. SmI_2 is a well-established reducing reagent in organic synthesis and is commercially available as a THF solution and in solid form [27]. Its THF solvate was synthesized according to Eq. (4) and was structurally characterized as a 7-coordinate $\text{SmI}_2(\text{thf})_5$ [70]. The less soluble $\text{YbI}_2(\text{thf})_2$ can be obtained analogously [27] and the ammonia complex is readily formed according to Eq. (5) [69]. $\text{TmI}_2(\text{dme})_3$ is the only soluble Tm(II) compound synthesized so far [Eq. (6)] [71]. A large-scale synthesis of SmBr_2 avoiding the expensive metal precursor has been accomplished according to the reaction sequence shown in Eq. (7) [68].

$$\text{Sm} \; + \; \text{ICH}_2\text{CH}_2\text{I} \xrightarrow{\text{THF}} \text{SmI}_2(\text{thf})_x \; + \; \text{CH}_2{=}\text{CH}_2 \tag{4}$$

$$\text{Yb} \; + \; 2\text{ NH}_4\text{I} \xrightarrow{\text{NH}_3(\text{liq})} \text{YbI}_2(\text{NH}_3)_x \; + \; \text{H}_2 \tag{5}$$

$$\text{TmI}_3 \; + \; \text{Tm} \xrightarrow[\Delta]{\text{DME}} 2\text{ TmI}_2(\text{dme})_3 \tag{6}$$

$$Sm_2O_3 \xrightarrow{\text{HBr}_{\text{aq.}}} SmBr_3 \text{x} 6H_2O \xrightarrow{\text{methyl orthoformate}} SmBr_3$$

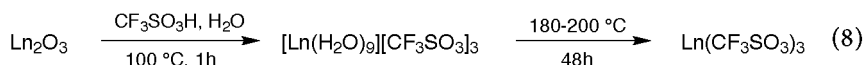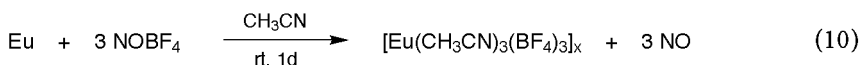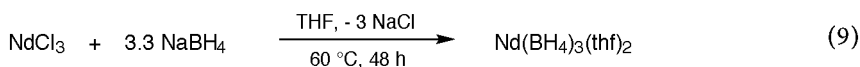$$SmBr_3 \xrightarrow{\text{Li, THF}} SmBr_2(\text{thf})_x$$

(7)

The complex $(\text{pyH})_2(\text{CeCl}_6)$ has been discussed as an alternative Ce(IV) precursor [72]. Pseudohalides such as thiocyanates should receive some attention as specific synthetic precursors due to their dual ligation mode [73]. Like the halides [74], their Ln(III) derivatives have been successfully employed as catalysts in organic transformations [75].

Other Inorganic Salts

Alternative inorganic precursors which are referred to in Scheme 2 are also available by treatment of lanthanide oxides Ln_2O_3 with the corresponding acid [76,77]. Nitrate ligands coordinate slightly stronger to the lanthanide centers compared to halides, but are reported to yield coarse precipitates of alkali nitrates in salt metathesis reactions [78]. Nitrates are also preferred as precursors in macrocyclic chemistry where they preferentially occupy the outer ligation sphere [7]. Strong complexation of doubly charged anions ($CO_3^{2-}>SO_4^{2-}$) causes a considerable decrease in solubility of the corresponding Ln_2X_3 and hence precludes their broad use as synthetic precursors [77]. Ln-fluorides [79] and phosphates are totally insoluble in solvents suitable for organometallics [4,15]. Pseudo-inorganic salts derived from superacids, in particular derivatives of triflate, contain weakly coordinating anions and were often found to be superior to lanthanide halides in salt metathesis reactions [80]. Anhydrous $Ln(OTf)_3$ can be easily obtained by thermal dehydration [Eq. (8)] [81]. Lanthanide triflates have attracted considerable attention as reuseable Lewis acidic catalysts in numerous carbon–carbon bond-forming reactions [82].

$$Ln_2O_3 \xrightarrow[\text{100 °C, 1h}]{\text{CF}_3\text{SO}_3\text{H, H}_2\text{O}} [Ln(H_2O)_9][CF_3SO_3]_3 \xrightarrow[\text{48h}]{\text{180-200 °C}} Ln(CF_3SO_3)_3 \quad (8)$$

Rare earth borohydrides obtained from the chlorides [Eq. (9)] [83] have been used in salt metathesis reactions and were found to be attractive for the generation of cationic species [84]. The presence of more weakly coordinated BF_4^- anions in $[Eu(MeCN)_3(BF_4)_3]_x$ which can be synthesized according to Eq. (10) promotes several catalytic transformations of non-heteroatom-substituted organic substrates, including the polymerization of styrene [85].

$$NdCl_3 + 3.3 \, NaBH_4 \xrightarrow[\text{60 °C, 48 h}]{\text{THF, - 3 NaCl}} Nd(BH_4)_3(\text{thf})_2 \quad (9)$$

$$Eu + 3 \, NOBF_4 \xrightarrow[\text{rt, 1d}]{\text{CH}_3\text{CN}} [Eu(CH_3CN)_3(BF_4)_3]_x + 3 \, NO \quad (10)$$

Cerium ammonium nitrate $[(NH_4)_2Ce(NO_3)_6, CAN]$, a key oxidizing agent, is the most common Ce(IV) precursor [86]. The use of acetylacetonates of cerium(IV) has been discussed [87] and $Ce(OTf)_4$ should also prove to be a valuable precursor [88].

Metals

Lanthanide metals which are conveniently prepared from the metal halides are commercially available in the form of ingots, chips (filings), foils and powders and are also handled as prominent synthetic precursors. For example, alkoxide complexes derived from cheap and low boiling alcohols are alternatively synthesized from metals under $HgCl_2$ catalysis [89]. Representative examples for transmetallation and transmetallation/ligand exchange reactions are given in Eqs. (11)–(13) [90]. Ammonia solutions of ytterbium and europium react with a variety of Brønsted acidic reagents according to Eq. (14) [91]. Metal oxidation/ligand transfer occurs in THF in the presence of catalytic [Eq. (15)] and stoichiometric amounts of iodine [Eq. (16)] [92]. "Lanthanide Grignard" reagents, formulated as "RLnI" are prepared in situ from the metal and the alkyl(aryl)halide in THF [Eq. (17)] [93]. Utilization of an extremely bulky alkyl ligand allowed the isolation of $\{Yb[C(SiMe_3)_3]I(OEt_2)\}_2$ according to a salt metathesis reaction [94].

$$Ln \quad + \quad 3\ TlCp \quad \xrightarrow[80\ °C,\ 20h]{THF} \quad LnCp_3(thf) \quad + \quad 3\ Tl \qquad (11)$$

$$Sm \quad + \quad Hg(C_6F_5)_2 \quad + \quad 2\ HNR_2 \quad \xrightarrow[12h]{THF} \quad Sm(NR_2)_2(thf)_4 \quad +$$
$$+ \quad Hg \quad + \quad 2\ HC_6F_5 \qquad\qquad\qquad (12)$$

$$Yb \quad + \quad Sn[N(SiMe_3)_2]_2 \quad \xrightarrow[80\ °C,\ 8h]{THF} \quad Yb[N(SiMe_3)_2]_2(thf)_2 \quad + \quad Sn \qquad (13)$$

$$Eu \quad \xrightarrow{NH_3(liq)} \quad Eu^{2+}(NH_3)_6 x2e^-(NH_3)_n \quad \xrightarrow[-H_2,\ -NH_3]{HR} \quad EuR_2(NH_3)_m \qquad (14)$$

$$Ln \quad + \quad 1.5\ ArSSAr \quad \xrightarrow[50\ °C,\ 48\ h]{I_2(!),\ THF,\ Py} \quad Ln(SAr)_3(py)_3 \qquad (15)$$

$$2\ Ln \quad + \quad Ph\diagdown\diagup\diagdown_{Ph} \quad + \quad 2\ I_2 \quad \xrightarrow[50\ °C,\ 48h]{THF} \quad Ph\!\!-\!\!\diagup\!\!\overset{LaI_2(thf)_2}{\underset{LaI_2(thf)_2}{|}}\!\!\diagdown\!\!-\!\!Ph \qquad (16)$$

$$Yb \quad + \quad CH_3I \quad \xrightarrow[-30\ °C]{THF} \quad \left[CH_3YbI \right] \qquad (17)$$
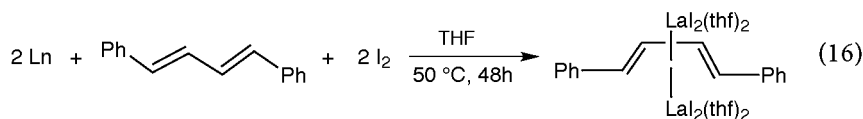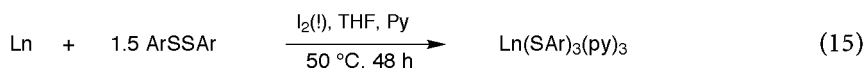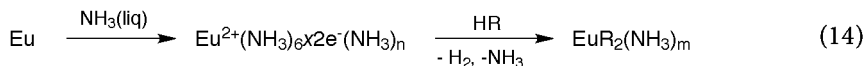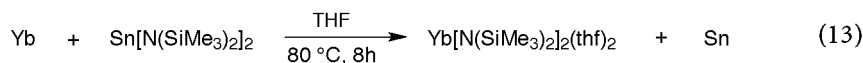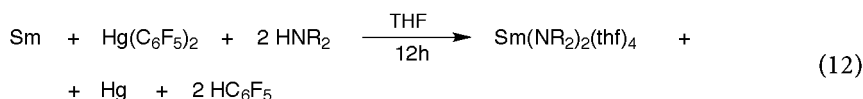
The co-condensation of electron-beam vaporized lanthanide metals with neutral (hetero-)aromatic molecules or 2,2-dimethylpropylidynephosphine (*t*BuCP) affords deeply colored compounds. The isolated, crystalline sandwich
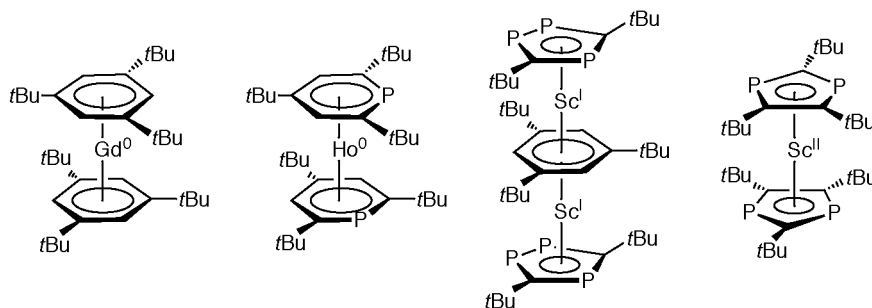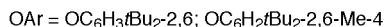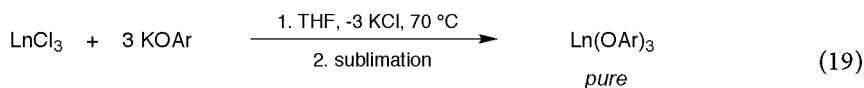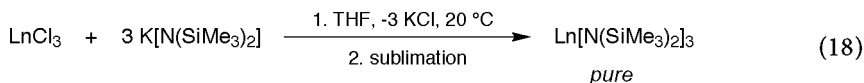
Fig. 5. Arene complexes of low-valent lanthanide elements obtained by co-condensation methods

and triple-decker complexes are thermally stable and exhibit lanthanide centers in the formal oxidation states Ln(0), Sc(I) and Sc(II) (Fig. 5) [95].
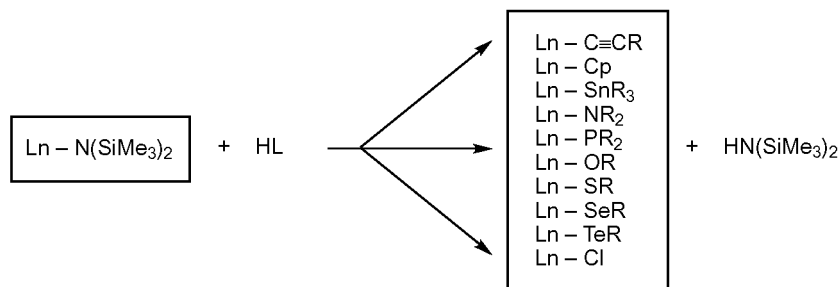
3.3
Metalorganic Reagents

According to Scheme 2, inorganics and pseudo-inorganics are suitable precursors for a variety of organometallic compounds. However, incorporation of alkali metal salts and *ate* complex formation according to the traditional metathesis route are often observed. As this is usually an undesired feature and particularly pronounced in rare earth alkyl [96], amide [97] and alkoxide chemistry [98] (Sect. 5.1), new synthetic routes involving well-defined metalorganic precursor compounds have been developed. Considering the (pseudo-)organometallic side of Scheme 2 (right), usually all of the compounds on this side are able to produce the neighboring systems on their left by Brønsted acid/base-type reactions, e.g. alkyls might readily react with amines, cyclopentadienes and alcohols to yield amide, alkoxide and cyclopentadienyl complexes, respectively. Lanthanide silylamide and aryloxide moieties qualify as versatile synthetic precursors due to high-yield and high-purity synthetic procedures. The preparation of their homoleptic derivatives is shown in Eqs. (18) and (19) [99,100].

$$LnCl_3 \ + \ 3\,K[N(SiMe_3)_2] \quad \xrightarrow[\text{2. sublimation}]{\text{1. THF, -3 KCl, 20 °C}} \quad Ln[N(SiMe_3)_2]_3 \qquad (18)$$
$$\textit{pure}$$

$$LnCl_3 \ + \ 3\,KOAr \quad \xrightarrow[\text{2. sublimation}]{\text{1. THF, -3 KCl, 70 °C}} \quad Ln(OAr)_3 \qquad (19)$$
$$\textit{pure}$$

OAr = $OC_6H_3tBu_2$-2,6; $OC_6H_2tBu_2$-2,6-Me-4

The Silylamide Route
Rare earth silylamide complexes have not only attracted enormous attention for the synthesis of precatalyst systems but also for the isolation of well-defined
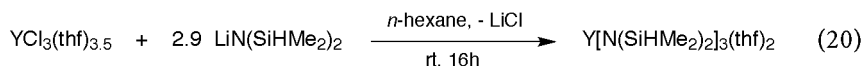
$$\boxed{\text{Ln} - \text{N(SiMe}_3)_2} \quad + \quad \text{HL} \quad \longrightarrow \quad \boxed{\begin{array}{l} \text{Ln} - \text{C}\equiv\text{CR} \\ \text{Ln} - \text{Cp} \\ \text{Ln} - \text{SnR}_3 \\ \text{Ln} - \text{NR}_2 \\ \text{Ln} - \text{PR}_2 \\ \text{Ln} - \text{OR} \\ \text{Ln} - \text{SR} \\ \text{Ln} - \text{SeR} \\ \text{Ln} - \text{TeR} \\ \text{Ln} - \text{Cl} \end{array}} \quad + \quad \text{HN(SiMe}_3)_2$$

Scheme 5. The *silylamide route*

compounds of relevance in precursor chemistry of ceramic and electronic materials, such as pure alkoxides [101,102]. The general redox stability of the lanthanide cations and the chemical robustness of the silylamide ligand has resulted in numerous ligand exchange reactions with substrate molecules of increased Brønsted acidity such as alcohols, phenols, cyclopentadienyls, acetylenes, phosphanes, and thiols as listed in Scheme 5 [103–113].

Factors which often make the *silylamide route* superior to traditional salt metathesis reactions are (i) the reaction in non-coordinating solvents due to the high solubility of the monomeric metal amides, (ii) mild reaction conditions often at ambient temperature, (iii) avoidance of halide contamination, (iv) ease of product purification [removal of the released amine along with the solvent under vacuum (bp $HN(SiMe_3)_2$: 125 °C)], (v) base-free products (coordination of the sterically demanding, released amine is disfavored), (vi) "quantitative yield", and (vii) the facile availability of mono- and heterobimetallic amide precursors.

A limiting factor of this specific amine elimination route is the steric bulk of the $[N(SiMe_3)_2]$ ligand, obvious in incomplete exchange reactions with similarly bulky ligands such as Cp*H [104], HOCtBu$_3$ [114] or highly substituted phosphanes [108]. In order to better cope with such sterically suppressed ligand exchange reactions the alternative silylamide precursor $Ln[N(SiHMe_2)_2]_3(thf)_2$, which can be prepared in high yield for all of the lanthanide elements [yttrium: Eq. (20)] [115], has been introduced.

$$\text{YCl}_3(\text{thf})_{3.5} \quad + \quad 2.9 \; \text{LiN(SiHMe}_2)_2 \quad \xrightarrow[\text{rt, 16h}]{n\text{-hexane, - LiCl}} \quad \text{Y[N(SiHMe}_2)_2]_3(\text{thf})_2 \qquad (20)$$

The bis(dimethylsilylamide) ligand $[N(SiHMe_2)_2]$ not only favors the attack of protic reagents by decreased steric bulk, but amine elimination is also affected by a decreased silylamide basicity, easier workup procedures (bp $HN(SiHMe_2)_2$: 93–99 °C) and the presence of an excellent spectroscopic probe ("Si-H"). According to this *"extended silylamide route"*, catalytically relevant complexes with salen [116], (substituted) linked-indenyl [117], and sulfonamide ligands [118] have been synthesized (Fig. 6). Such controlled ligand associations, which are
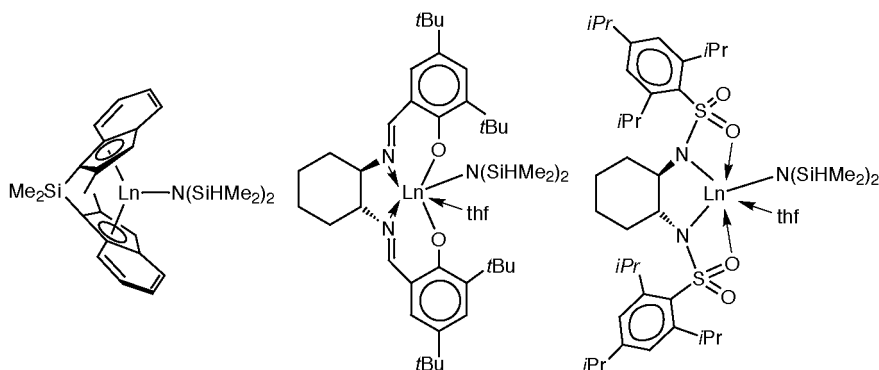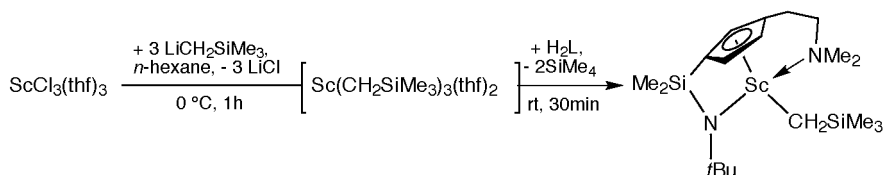
Fig. 6. C_2-symmetric rare earth complexes according to the extended silylamide route


Scheme 6. In situ generation of a reactive alkyl precursor

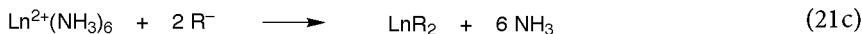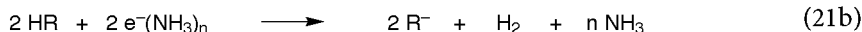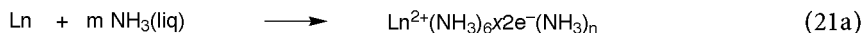proposed as proceeding via THF dissociation, are not obtained with the $Ln[N(SiMe_3)_2]_3$ system.

The application of the more basic $Ln(NiPr_2)_3(thf)$ as a metalorganic precursor compound is controversial [119] because its availability is hampered by ate complexation [Sect. 5.1, $LiLn(NiPr_2)_4$] and enhanced thermal instability (decomposition at 100 °C/10^{-4} Torr) [120]. An efficient alkane elimination reaction utilizing the in situ formed alkyl species $Ln(CH_2SiMe_3)(thf)_2$ produced complexes with linked amido cyclopentadienyl ligands (Scheme 6) [121]. However, the thermal instability of $Ln(CH_2SiMe_3)(thf)_2$ and ate complex formation seem to be limiting factors [122].

The *silylamide route* can also be applied to lanthanide(II) chemistry (Scheme 7). Although the well-characterized complexes $Ln[N(SiMe_3)_2]_2(thf)_2$ exhibit enhanced steric flexibility [123], the scope of exchange reactions is now limited by the reductive properties of Sm(II). For example, Sm(II) amides tend to get oxidized by enolizable alcohols [124]. However, aryloxides of type $Sm(OAr)_2(thf)_x$ have been isolated and ate complexation as evidenced in $[KSm(OC_6H_3-2,6-tBu_2)_3(thf)]_n$ proves to be a stabilizing factor [125]. According to this latter approach, mixed metallic complexes can be obtained by retention of the original metal ligand composition. Partially exchanged heteroleptic complexes such as $\{KSmCp^*_2[N(SiMe_3)_2](thf)_2\}_n$ are available due to steric restrictions [126]. Eu(II) and Yb(II) silylamides are accessible to all of the exchange reactions listed in Scheme 5 [127].
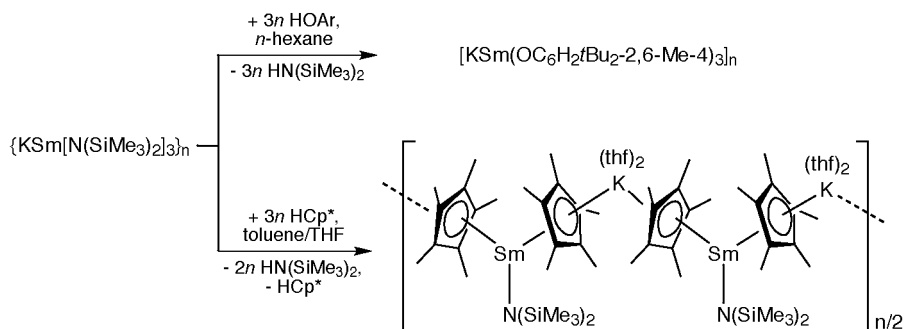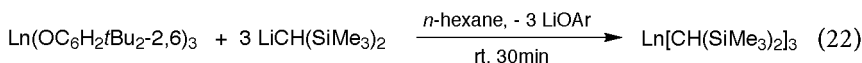
Scheme 7. Heterobimetallic Sm(II) complexes according to the *silylamide route*

Organometallic derivatives of europium and ytterbium are also readily formed via reactions in liquid ammonia. The active species in these reactions are the hexaammine complexes and the only byproducts are hydrogen and ammonia [Eq. (21a-c)]. According to this procedure, the compounds $EuCp_2$ [128], Yb-$Cp^*_2(NH_3)_x$ [91], $Ln(COT)$ (Ln=Eu,Yb) [129, 130], $Eu(C{\equiv}CMe)_2$ [131], $Eu(Ph_2)_2$ [132], $Yb(OC_6H_2tBu_2\text{-}2,6\text{-}Me\text{-}4)_2(thf)_3$ [90c], LnX_2 (Ln=Eu, Yb; X=Cl, Br, I) [133] and decaborates, e.g. $(NH_3)_xYb(B_{10}H_{14})$ [134] have been synthesized.

$$Ln \ + \ m \ NH_3(liq) \longrightarrow Ln^{2+}(NH_3)_6 x2e^-(NH_3)_n \qquad (21a)$$

$$2 \ HR \ + \ 2 \ e^-(NH_3)_n \longrightarrow 2 \ R^- \ + \ H_2 \ + \ n \ NH_3 \qquad (21b)$$

$$Ln^{2+}(NH_3)_6 \ + \ 2 \ R^- \longrightarrow LnR_2 \ + \ 6 \ NH_3 \qquad (21c)$$

## Generation of Lanthanide Alkyl Bonds

Lanthanide alkyl compounds are important alkyl transfer reagents and initiate a variety of catalytic reactions. The transformation of lanthanide alkoxide bonds to lanthanide alkyl bonds seems to be an attractive alternative to the alkylation of lanthanide halides with alkali metal alkyl compounds. For example, the *aryloxide route* affords homoleptic lanthanide alkyls in good yield [Eq. (22)] [135].

$$Ln(OC_6H_2tBu_2\text{-}2,6)_3 \ + \ 3 \ LiCH(SiMe_3)_2 \ \xrightarrow[\text{rt, 30min}]{n\text{-hexane, - 3 LiOAr}} \ Ln[CH(SiMe_3)_2]_3 \qquad (22)$$

Due to the high solubility of the starting and the resulting rare earth complexes, the reaction can be conducted in nonpolar solvents from which the insoluble alkali aryloxides can easily be separated. However, this type of kinetically controlled metathesis reaction is very sensitive towards the reaction conditions including the type of alkoxide (aryloxide) ligand, type of metal, number and type of co-ligands, stability and solubility of the eliminated alkali metal alkoxide (aryloxide), solvent, temperature, etc. As a result, incomplete ligand exchange, exchange of the co-ligand, ate complexation, exchange equilibria and ligand re-

distribution can occur. Scheme 8 gives an idea of the complexity of these alkoxide-derived alkylation reactions [136–139]. Acetylacetonate complexes have been discussed as alternative alkyl precursors [87].

Aluminum alkyls, in particular trimethylaluminum, produce chelating alkyl alkoxide moieties, $[(\mu\text{-}OtBu)AlMe_2(\mu\text{-}Me)]$, via Lewis acid/base-pair formation [140,141]. In the reaction with $Y_3(OtBu)_7Cl_2(thf)_2$, $AlMe_3$ simultaneously acts as a powerful denucleation reagent tolerating ethereal solvents such as THF at the lanthanide center (Scheme 9). Reaction products such as $LnCl_3(dme)_2$ arise from ligand redistributions (Sect. 5.3). The homoleptic complex $Ln[(\mu\text{-}OtBu)AlMe_2$
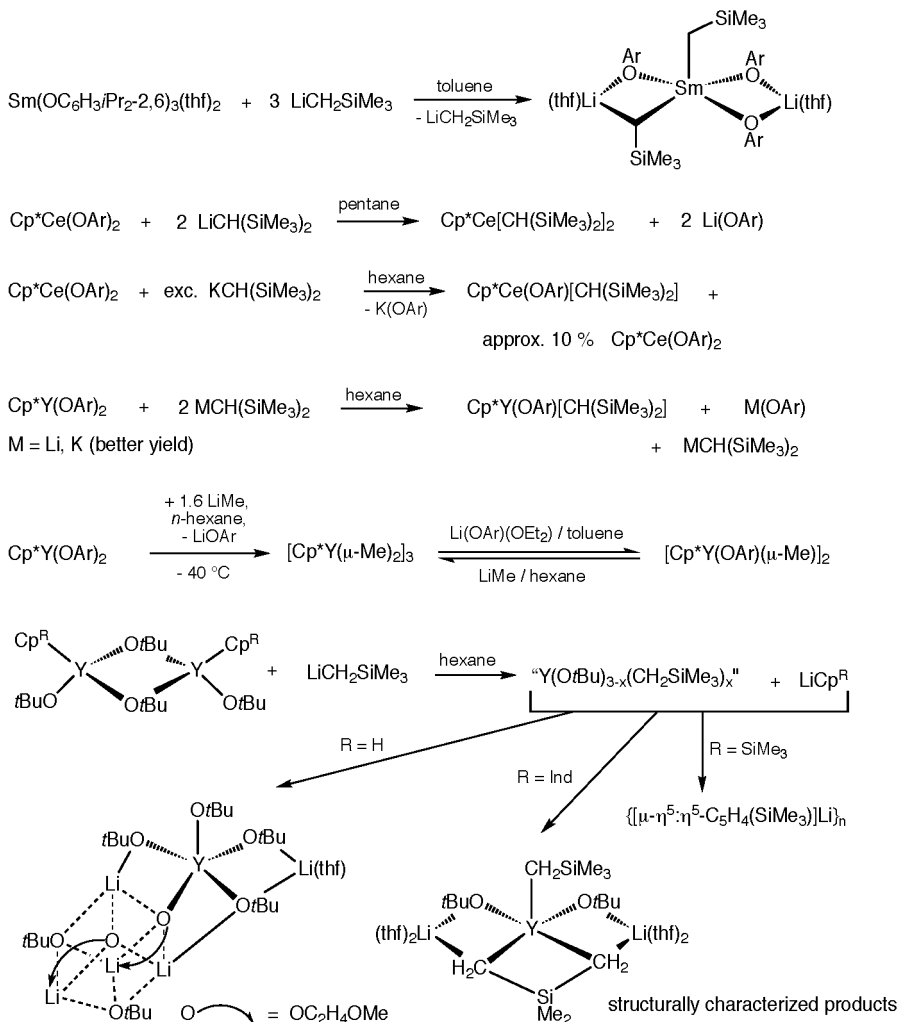
Scheme 8. Reaction behavior of lanthanide aryloxide and alkoxide complexes towards alkali metal alkyl reagents $(OAr=C_6H_3tBu_2\text{-}2,6)$

Y$_3$(OtBu)$_7$(Cl)$_2$(thf)$_2$

3 AlMe$_3$,
hexane
rt, 12h

→ products

hexane extract

THF extract
(DME)
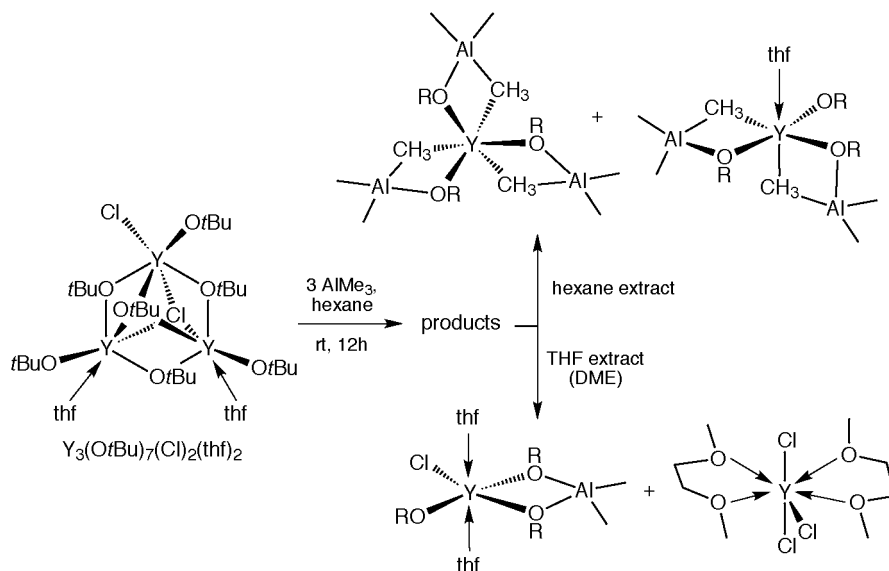
Scheme 9. Reaction of AlMe$_3$ with a mixed alkoxide halide cluster

4 MMe$_3$,
- 3 LiCl

→ Ln[(μ-Me)$_2$MMe$_2$][(μ-Me)(μ-NMe$_2$)MMe$_2$]$_2$ + 0.5 [Me$_2$NMMe$_2$]$_2$

Ln(NMe$_2$)$_3$(LiCl)$_3$

hexane, rt

excess MMe$_3$,
- 3LiCl

+ 1.5 [Me$_2$NMMe$_2$]$_2$

Ln[(μ-Me)$_2$MMe$_2$]$_3$
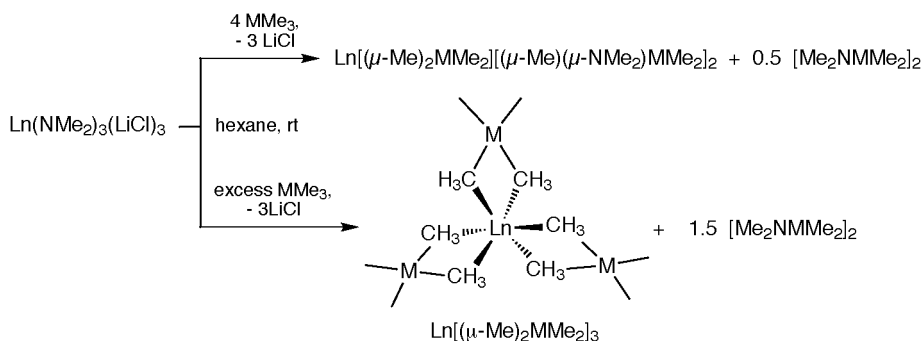
Scheme 10. Alkylation of lanthanide amide complexes with group 13 metal alkyls (M=Al, Ga)

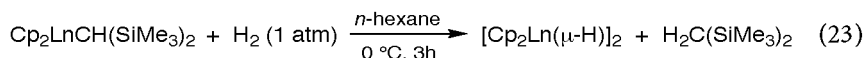(μ-Me)]$_3$ can be obtained as the sole product from the reaction of AlMe$_3$ with Ln$_3$(OtBu)$_9$ [142].

Extended alkylation is observed when lanthanide amide complexes are used as synthetic precursors [107,143]. The formation of a strong group 13 metal–N(amide) bond promotes this type of alkylation reaction. Depending on the stoichiometry, the reaction of MMe$_3$ (M=Al, Ga) with Ln(NMe$_2$)$_3$(LiCl)$_3$ yields partially or peralkylated species (Scheme 10). Again, the reactivity is determined by steric factors. For example, the sterically encumbered La[N(SiMe$_3$)$_2$]$_3$ does not show any tendency to form a Lewis acid/base adduct with group 13 metal alkyls, a prerequisite for subsequent alkylation under these
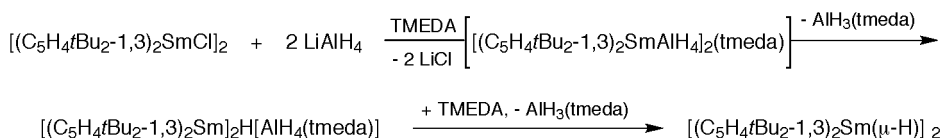
conditions [115]. However, peralkylated products are obtained from $Ln[N(SiHMe_2)_2]_3(thf)_2$, $Sm[N(SiMe_3)_2]_2(thf)_2$, and $KSm[N(SiMe_3)_2]_3$ [8,115].

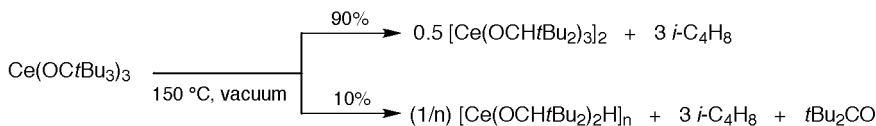### Generation of Lanthanide Hydride Bonds

Organolanthanide hydride complexes are also key reagents in rare earth catalysis. The highly reactive lanthanide hydride bonds not only serve as catalytic initiators but are also often assumed key intermediates in catalytic reactions such as the hydrosilylation [144] and olefin polymerization reaction (β-H elimination) [145]. The hydrogenolysis of alkyl complexes is a favorable route for synthesizing lanthanide hydride bonds [Eq. (23)] [146]. However, small changes in the size of the metal, the size of the alkyl group, solvent, degree of association of the complex, or type of co-ligand cause substantial changes in reactivity [137,146].
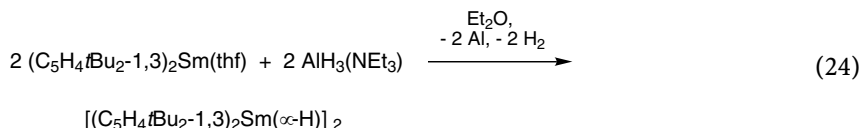
$$Cp_2LnCH(SiMe_3)_2 + H_2 \text{ (1 atm)} \xrightarrow[\text{0 °C, 3h}]{n\text{-hexane}} [Cp_2Ln(\mu\text{-H})]_2 + H_2C(SiMe_3)_2 \quad (23)$$

Although solid state structures of these complexes exclusively display bridging "$Ln(\mu\text{-H})_nLn$" moieties [4], a fluxional behavior in solution with terminal Ln–H bonds as the reactive species has been suggested [147]. $LiAlH_4$ acts as an elegant hydride transfer reagent and depending on the nature of the metal and donor ligand, as well as the cyclopentadienyl substitution, dinuclear species are formed (Scheme 11) [148]. Similar unsolvated dinuclear species were obtained from the reduction of alane by Sm(II) organometallics [Eq. (24)] [149]. Lanthanide hydride species can also be generated by thermal treatment of lanthanide alkyl complexes such as Cp_2LntBu [150] or by salt metathesis reactions employing NaH [151]. The thermal decomposition of the sterically crowded lanthanide alkoxide complex $Ln(OCtBu_3)_3$ produced a bridged hydride species as a side product (Scheme 12) [109].

$$[(C_5H_4tBu_2\text{-}1,3)_2SmCl]_2 + 2\,LiAlH_4 \xrightarrow[\text{- 2 LiCl}]{TMEDA} \Big[(C_5H_4tBu_2\text{-}1,3)_2SmAlH_4]_2(tmeda)\Big] \xrightarrow{\text{- AlH}_3(tmeda)}$$

$$[(C_5H_4tBu_2\text{-}1,3)_2Sm]_2H[AlH_4(tmeda)] \xrightarrow{\text{+ TMEDA, - AlH}_3(tmeda)} [(C_5H_4tBu_2\text{-}1,3)_2Sm(\mu\text{-H})]_2$$

Scheme 11. Generation of lanthanide hydride bonds via a salt metathesis reaction

$$Ce(OCtBu_3)_3 \xrightarrow{\text{150 °C, vacuum}} \begin{cases} \xrightarrow{90\%} 0.5\,[Ce(OCHtBu_2)_3]_2 + 3\,i\text{-}C_4H_8 \\ \xrightarrow{10\%} (1/n)\,[Ce(OCHtBu_2)_2H]_n + 3\,i\text{-}C_4H_8 + tBu_2CO \end{cases}$$

Scheme 12. Generation of lanthanide hydride bonds via thermal degradation

$$2 \ (C_5H_4tBu_2\text{-}1,3)_2Sm(thf) \ + \ 2 \ AlH_3(NEt_3) \xrightarrow[\quad\quad\quad]{\substack{Et_2O, \\ -\ 2\ Al,\ -\ 2\ H_2}} \tag{24}$$

$$[(C_5H_4tBu_2\text{-}1,3)_2Sm(\propto\text{-}H)]_2$$

Generation of Cationic Organolanthanide Species

Several routes are currently applied to synthesize cationic organolanthanide species, including the halide abstraction from heteroleptic Ln(III) compounds [Eq. (25)] [152], the oxidation of divalent metallocenes [Eqs. (26) and (27)] [153], the protolysis of lanthanide alkyl and amide moieties [Eqs. (28) and (29)] [154,155], and anion exchange [Eqs. (30) and (31)] [84,156]. In the absence of a coordinating solvent such extremely electrophilic species attain stabilization via arene i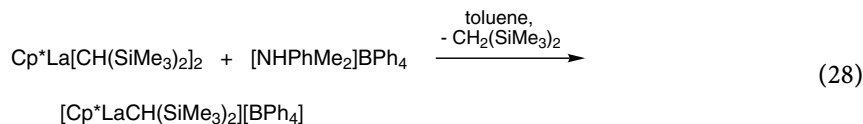nteractions with the BPh_4^- anion (Sect. 5.1) [153b]. Cationic rare earth species have been considered as promising candidates for Lewis acid catalysis [157].

$$[C_5H_3(SiMe_3)_2\text{-}1,3]_2CeI(NCMe)_2 \ + \ AgBF_4 \xrightarrow[rt]{THF,\ -\ AgI} \tag{25}$$

$$\{[C_5H_3(SiMe_3)_2\text{-}1,3]_2Ce(NCMe)_2\}[BF_4]$$

$$Cp*_2Sm(thf)_2 \ + \ AgBPh_4 \xrightarrow{THF} \ [(Cp*_2Sm(thf)_2][BPh_4] \ + \ Ag \tag{26}$$

$$Cp*_2Sm \ + \ AgBPh_4 \xrightarrow{toluene} \ [Cp*_2Sm][BPh_4] \ + \ black\ solids \tag{27}$$

$$Cp*La[CH(SiMe_3)_2]_2 \ + \ [NHPhMe_2]BPh_4 \xrightarrow[\quad\quad\quad]{\substack{toluene, \\ -\ CH_2(SiMe_3)_2}} \tag{28}$$

$$[Cp*LaCH(SiMe_3)_2][BPh_4]$$

$$(salen)Y[N(SiHMe_2)_2](thf) \ + \ [NHMe_3]BPh_4 \xrightarrow[rt]{\substack{THF,\ -\ NMe_3 \\ -\ HN(SiHMe_2)_2}} \tag{29}$$

$$[(salen)Y(thf)_3][BPh_4]$$

$$(COT)Nd(BH_4)(thf)_2 \ + \ [NHEt_3]BPh_4 \xrightarrow[rt]{THF} \ [(COT)Nd(thf)_4][BPh_4] \ + \tag{30}$$

$$+ \ "[NHEt_3]BH_4"$$

$$SmCl_3(H_2O)_6 \xrightarrow[\text{2. NaBPh}_4/H_2O,\ -\ NaCl]{\text{1. KL/MeOH, - 2 KCl}} \ [SmL_2][BPh_4] \tag{31}$$

$$L = tris[3\text{-}(2\text{-}pyridyl)\text{-}pyrazol\text{-}1\text{-}yl]hydroborate$$

3.4
Thermal Stability

Despite the kinetic lability of the Ln–X σ-bonds (even the thermodynamically very stable Ln–OR bond undergoes rapid ligand exchange reactions [158]), organolanthanide compounds are thermally robust over a wide range of temperature [99,100,102,104,159–165]. Thermal stability is important for conducting ligand exchange reactions and catalytic transformations at elevated temperatures [1,22]. The sublimation behavior is a criterion of thermal stability, and is frequently consulted to judge the suitability of volatile molecular precursors for chemical vapor deposition techniques (Fig. 7).

Bulky ligands affect the ionic nature of the polarized Ln–X bond by minimizing polar interactions (intra- and intermolecular) and optimizing volatility by the concept of steric shielding. The detection of isolated molecules instead of salt-like arrangements in the solid state confirms this trend. The polarizing effect can also be reduced by introduction of donor-functionlized ligands which can bring about charge transfer to the metal cation. Decomposition pathways can be sterically blocked by filling the coordination sphere of the metal with large ligands. However, sterically overcrowded ligands may degradate at elevated temperature as illustrated for the $Ln(OCtBu_3)_3$ system [109].

4
Ligand Concepts

Ligand design occupies a pivotal role in organolanthanide chemistry. The nature of the ligand, including its size, basicity, and functionalization, promptly affects complex features such as (mono)nuclearity, cation size and electrophilicity. Prolific metal cation/ligand synergisms impart novel reactivity patterns which can
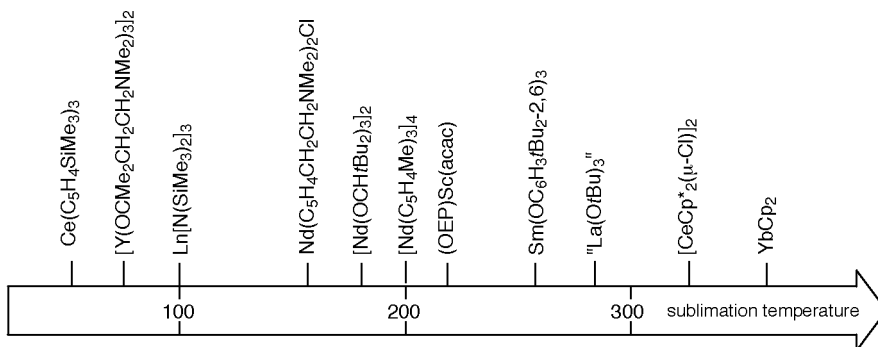

Fig. 7. Sublimation behavior of various lanthanide complexes at 10^{-3} mbar (*OEP* 2,3,7,8,12, 13,17,18-octa(ethyl)porphyrin; *acac* acetylacetonate)

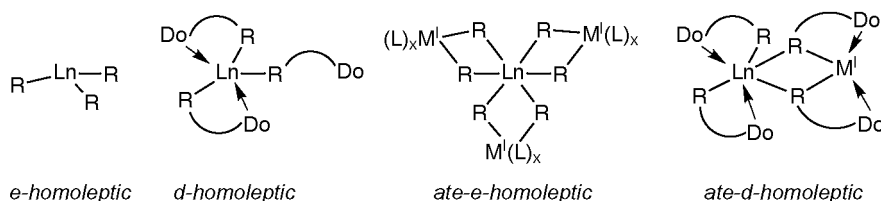e-homoleptic   d-homoleptic   ate-e-homoleptic   ate-d-homoleptic

Fig. 8. Modes of homoleptic Ln(III) coordination (*Do* donor functionality)

be of interest in, for example, ligand-enhanced stereoselective catalysis [166]. Therefore, ligand classification and adaptation deserve particular attention.
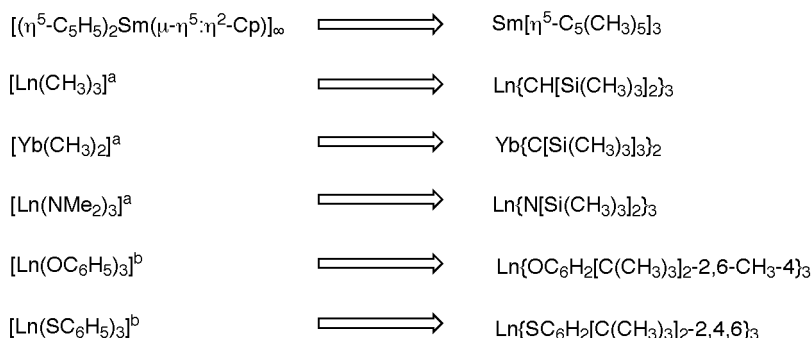
Assuming the ligand interaction to be of electrostatic origin, optimal charge balance of the lanthanide(III) cations should be achieved by three stable anionic ligands. Identical anions accomplish so-called homoleptic systems which can be of neutral type $(MR_n)_x$ or ate type $[MR_n]^{z-}[X_m]^{z+}$ [167]. Homoleptic compounds can be further classified as to whether the ligands are coordinatively equally (*e-homoleptic*) or differently (*d-homoleptic*) attached to the metal center (Fig. 8). The *d-homoleptic* mode is found in oligomeric systems where both terminal and bridging ligands are present; however, they are also found in monomeric complexes which contain functionalized ligands. Here, steric oversaturation can prevent the formation of *e-homoleptic* coordination [31,168].

Heteroleptic organolanthanide complexes containing reactive Ln–X bonds and stabilizing ancillary ligands are key precursor compounds in catalytic transformations. Mononuclearity is usually a prerequisite for both good solubility and reactivity. Utilization of bulky ligands, ate complexation, and donor functionalization are applicable procedures for generating mononuclear complexes.

4.1
Steric Bulk and Donor Functionalization

Scheme 13 emphasizes the effect of sterically demanding groups on the generation of homoleptic mononuclear complexes. This modification often gives access to classes of compounds which are not isolable/defined in the presence of correspondingly small ligands. Various examples feature both different Ln–X bonds and different oxidation states [169]. Structurally characterized Ln–C bonded homoleptic systems include alkyl [94,135], cyclopentadienyl [31,170], pentadienyl [171], pentamethylcyclopentadienyl [172], indenyl [173], cyclooctatetraenyl [80e], (aza)allyl [174] and arene derivatives [26]. Representative examples of pseudo-organometallics containing Ln–N bonds comprise silylamide, azabutadiene, benzamidinate and porphyrin complexes [114,175–178]. Aryloxide, alkoxide, β-diketonate and Schiff base ligands can stabilize homoleptic mononuclear Ln–O derived complexes [101, 179–182]. Derivatives featuring phosphorus and sulfur bonds include alkyl phosphides [183] and aryl and alkyl sulfides [90c,184].

$[(\eta^5\text{-}C_5H_5)_2Sm(\mu\text{-}\eta^5{:}\eta^2\text{-}Cp)]_\infty$ $\Longrightarrow$ $Sm[\eta^5\text{-}C_5(CH_3)_5]_3$

$[Ln(CH_3)_3]^a$ $\Longrightarrow$ $Ln\{CH[Si(CH_3)_3]_2\}_3$

$[Yb(CH_3)_2]^a$ $\Longrightarrow$ $Yb\{C[Si(CH_3)_3]_3\}_2$

$[Ln(NMe_2)_3]^a$ $\Longrightarrow$ $Ln\{N[Si(CH_3)_3]_2\}_3$

$[Ln(OC_6H_5)_3]^b$ $\Longrightarrow$ $Ln\{OC_6H_2[C(CH_3)_3]_2\text{-}2,6\text{-}CH_3\text{-}4\}_3$

$[Ln(SC_6H_5)_3]^b$ $\Longrightarrow$ $Ln\{SC_6H_2[C(CH_3)_3]_2\text{-}2,4,6\}_3$

Scheme 13. Tractable, mononuclear species via steri cally bulky ligands ([a]compound not known/ not stable; [b]degree of agglomerization not determined)

   The attachment of potentially coordinating groups produces donor-function-alized ligands and is a popular approach to fine-tuned ancillary ligands. This is particularly appealing in organolanthanide chemistry [185], considering the large size of the lanthanide cations and their preference for high coordination numbers. Intramolecular ring formation via "dative bonds" [186] according to the HSAB concept stabilizes mononuclear complexes via the effect of chelation and entropy. Ligand-bonded donor groups successfully compete with donating solvent molecules for coordination sites, implying improved thermal behavior by suppressing oligomerization during heating and sublimation. The presence of intramolecularly active donor functionalities affects the polarity of the lan-thanide–counterion bond by more or less pushing electron density into the met-al. As a result strong donor groups will significantly decrease the reactivity of an adjacent, kinetically labile Ln–X bond, but on the other hand enhance its stabil-ity against hydrolysis. Hence, the balance of donor strength is important for the production of a flexible coordination mode, revealed by "arm on – arm off" processes. Such *hemilabile ligands* are proposed as directing the approach of or-ganic substrates in catalytic transformations [187]. In the absence of ring strain the bond strength of such an intramolecular coordination resembles that of the corresponding intermolecular one [188]. For example, the strength of an in-tramolecular hard "←OR_2" coordination will be in the range of 5–7 kcal/mol as determined for intermolecular THF coordination [41].
   Figure 9 outlines general strategies of donor functionalization applied in lan-thanide alkyl [189–193], amide [194–196] and alkoxide chemistry [180,197,198]. Hard donor functionalities such as NMe_2 and OMe dominate this scenario and it is often the combination of steric bulk and donor ligation which leads to the envisaged mononuclear species. Donor functionalization of alkyl ligands proved to be successful even in stabilizing lanthanide alkyl bonds in a low-valent Sm(II) species [191]. Allylic moieties are also very effective in stabilizing low aggregated organolanthanide species as evidenced in mononuclear homoleptic phosphi-
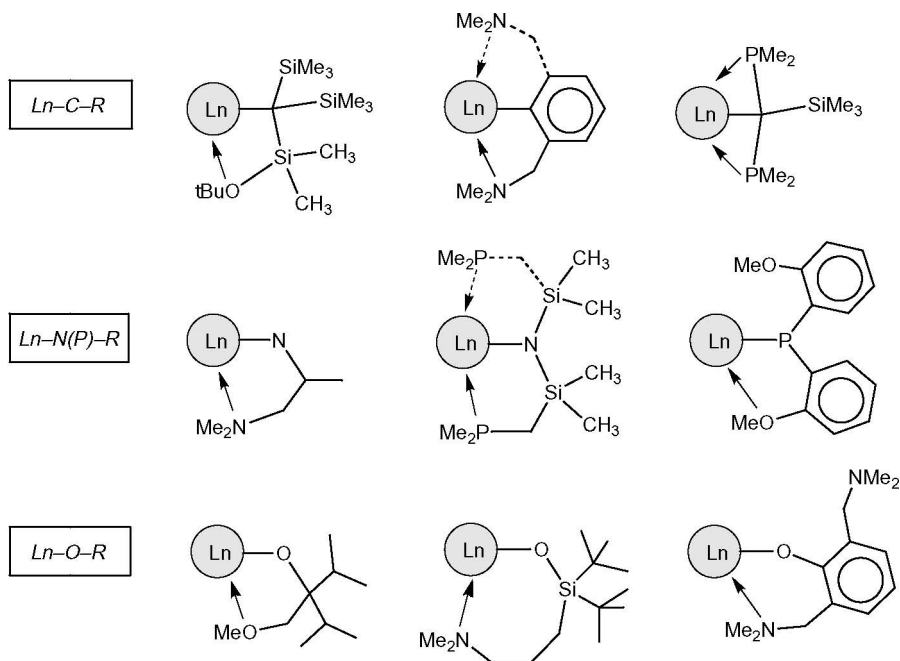
Fig. 9. Donor functionalization of monovalent rare earth complexes
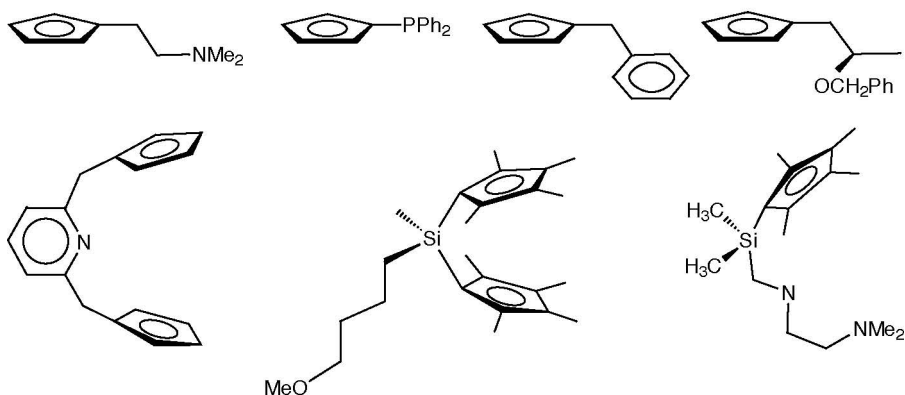

Fig. 10. Functionalization of cyclopentadienyl ligands

nomethanide [199], benzamidinate [200] and azaallyl complexes [177]. Multiple functionalization displays another option. As revealed in aryl [193] and silylamide derivatives [195], donor moieties flank the central bonding unit in a potentially tridentate chelating array.

Not surprisingly, donor functionalization has been extensively applied to tailor cyclopentadienyl ligands (Fig. 10). In addition to the attachment of one pendant donor arm [160, 201], functionalization via donor-linked bis(cyclopentadienyl) ligands [202], including donor-tethered silicon bridges [203], and donor functionalized chiral side chains are found [204]. Only a few examples feature soft donor functionalities such as phosphines [205] and arenes [206].

4.2
Ancillary Ligands

Various terms including "spectator ligand", "auxiliary ligand" or "ancillary ligand" are used to characterize the portion of the ligand sphere which is not directly involved in basic reactivity steps such as insertion or ligand exchange reactions. Primarily, ancillary ligands serve to prevent oligomerization or polymerization of electronically and coordinatively unsaturated derivatives, and to impart kinetic stability for otherwise highly reactive species. The mononuclearity, chemical robustness and rigidity anticipated are common attributes of a well-defined precatalyst system. Furthermore, ancillary ligands can direct catalytic processes if their bulkiness causes metal shielding and steric constraints, if differently polarized Ln–X bonds affect the electrophilicity of the metal center, or if they exhibit a reservoir for chirality and additional flexible coordination sites.

Hence, synthetic organolanthanide chemistry puts the main emphasis on the adaption of prevailing precatalyst types to the requirements of highly enantioselective catalysis. This is impressively demonstrated by tied-back cyclopentadienyl complexes [207], even water-stable BINOL systems [43], and fluorinated β-diketonate complexes (Fig. 11) [208].
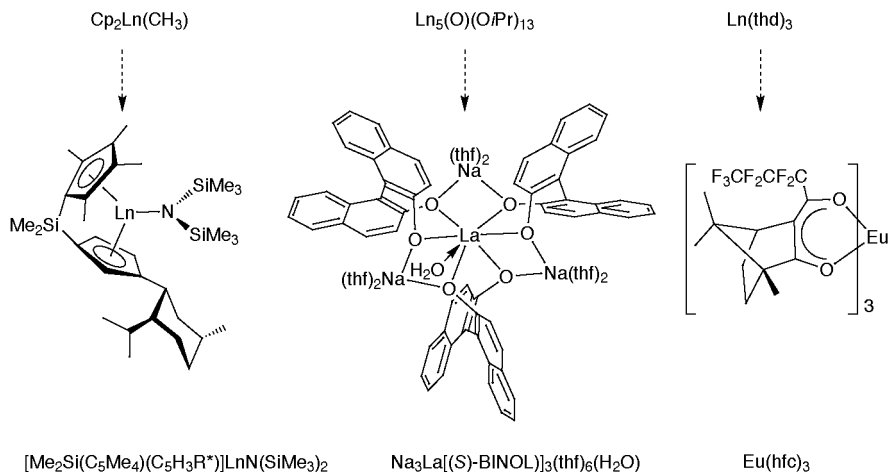

Fig. 11. Development of sophisticated ligand environments for enantioselective catalysis [*thd* 2,2,6,6-tetramethyl-3,5-heptanedione, *hfc* 3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]
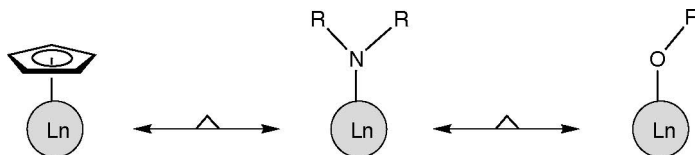
Fig. 12. Amide and alkoxide moieties as cyclopentadienyl-analogous ligands

Cyclopentadienyl derivatives and related systems such as indenyl and fluorenyl still play a dominant role in ligand fine-tuning. However, ligand design has gradually reached a high level of variety and sophistication, e.g. as presented by the new generation of group 4 metal "non-metallocene" catalysts (for olefin polymerization) [209,210]. In particular, chelating nitrogen-containing counter ligands have become the focus of much attention [209]. Similar to the related alkoxide ligands [210], they offer a lower formal electron count, thus rendering a more electrophilic and therefore potentially more active catalyst fragment (Fig. 12) [37]. Ancillary ligands, reported for Ln(III) species, can be classified according to their charge (valency) and coordination mode (Figures 13–15).

Monovalent Ligands
Numerous mono-charged cyclopentadienyl substitutes have been discussed in relevance to the catalysis topic. The attachment of one or two of such ligands is easily perfomed and may render two or one reactive sites, respectively. The resulting ligand sphere offers enhanced steric flexibility, and kinetic inertness of the monovalent ancillary ligand is often achieved via chelation through charge delocalization or donor functionalization. The stability of the resulting complexes, however, can be affected by ligand redistribution (disproportionation) and formation of the homoleptic system (Sect. 5.3). A representative selection of this ligand type is shown (Fig. 13), comprising N,N'-bis($tert$-butyl)glyoxaldiimine [(dad)Li]$^-$ [211], N-isopropyl-2-(isopropylamino)troponimine [(iPr)$_2$ati] [212], substituted benzamidinates [213], substituted tris(pyrazolyl)borates Tp-R$_x$ [214], (N,O-bis($tert$-butyl) (alkoxydimethylsilyl)amide [215], tri($tert$-butyl)methoxide (tritox) [102], substituted aryloxides [137], tri($tert$-butyl)siloxide (silox) [102,216] and functionalized siloxide ligands [217].

Divalent Ligands
Heteroleptic complexes derived from doubly charged, "*linked*" ligands constitute a class of well-defined metallocene-analogous precatalyst species. Various C_1- and C_2-symmetric members of the bis(cyclopentadienyl) fragment have been reported [218], including linked amido-cyclopentadienyl [219] and dihydroanthracene-cyclopentadienyl ligands [220] (Fig. 14). Such divalent ligands when coordinated in a chelating fashion provide a strongly bonded, rigid backbone which not only imparts kinetic stability but is also a prerequisite for asymmetric induction at the metal center. By nature, the synthesis of these ancillary ligands is more costly/lengthy and subsequent complex preparations may re-
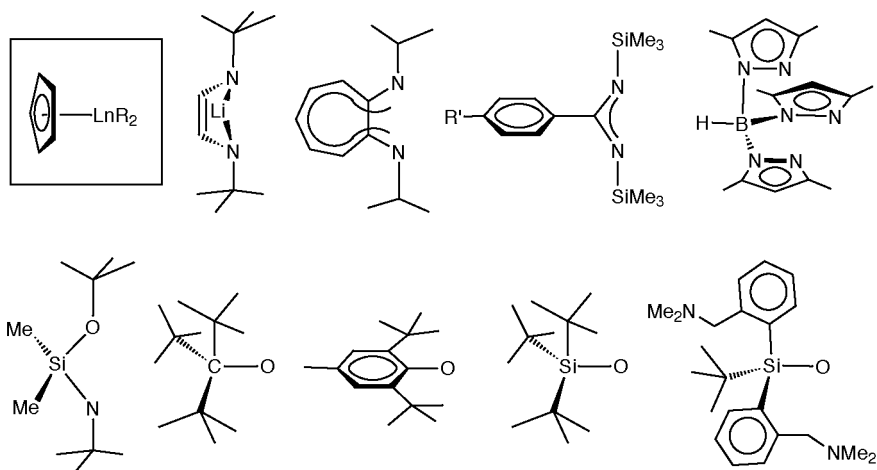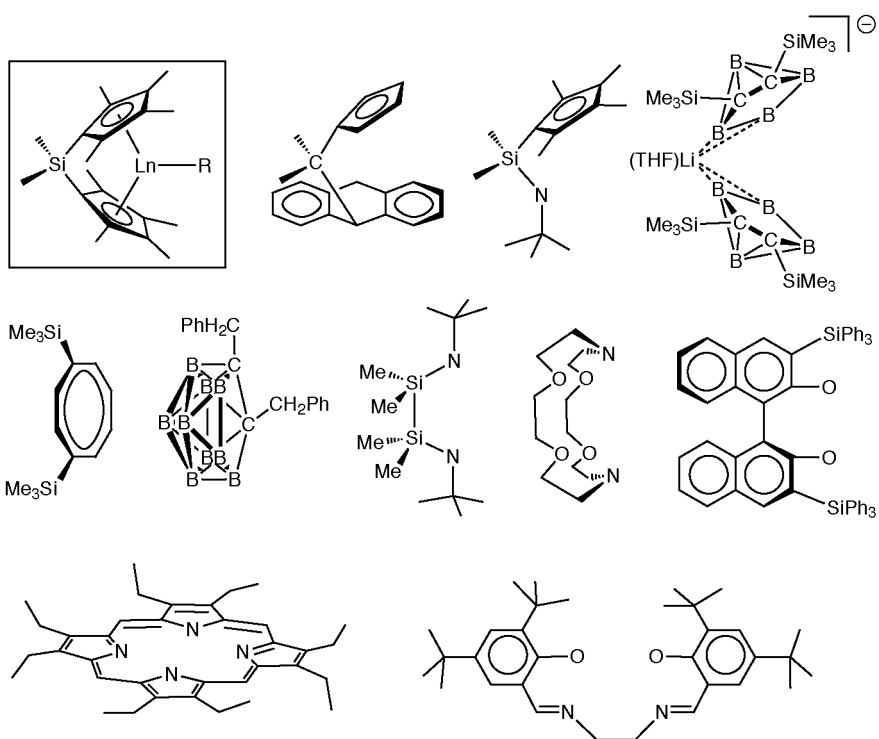
Fig. 13. Monovalent ancillary ligands

Fig. 14. Divalent ancillary ligands

quire alternative routes to avoid oligomerization by ligand bridging [116–118]. The remaining Ln(III)–R bond, typically an alkyl, hydride or amide moiety, displays a reactive site whose kinetic profile can be stabilized upon variation of the bite angle and chelate ring size of the ancillary ligand, respectively [37]. Together with diamide [221,222], biphenol or BINOL ligands [223,224], salen [116] and sulfonamide ligands [118] have been discussed as alternative spectator environments. The latter can easily be obtained in enantiomerically pure form. *Template*-type ligands such as cyclooctatetraenyl [225] and porphyrin [226] have been shown to be very effective in stabilizing mononuclear complexes. In particular, porphyrin–metal moieties are rather robust and less moisture-sensitive. Carborane derivatives have been employed both in the form of "lithium"-linked [227] and template-type ligands [228].

Trivalent Ligands
Complexes derived from triply charged ligands formally correspond to the homoleptic tris(cyclopentadienyl) complexes $LnCp_3$. These compounds can be of relevance in Lewis acid catalysis where their activity is directed by the formation of Lewis acid (catalyst)/base (substrate) pairs [229]. Hence, metal–ligand bond disruption and formation processes are pushed into the background. Linked cyclopentadienyl-carborane ligands form mononuclear *commo* (sandwiched) metallacarborane complexes [230]. Highly functionalized podate ligands such as triamidoamine ("azatrane") [231] and tribenzyltrifluoroacetoacetate [232] produce formally 4- and 6-coordinated complexes, respectively (Fig. 15). A dinuclear composition has been proven for Ln(III) complexes of the trivalent oligosilsesquioxane ligand, $T_7(OH)_3$ [233]. These incompletely condensed ligands
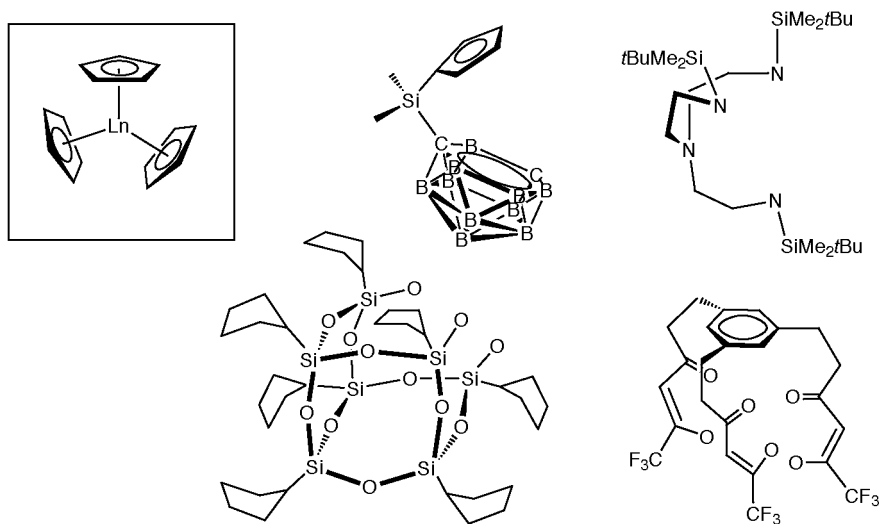

Fig. 15. Trivalent ancillary ligands

appear to be highly electron withdrawing and are currently being studied as models for silica surfaces [234].

4.3
Immobilization – "Supported Ligands"

The ligand sphere can also be manipulated by immobilization (grafting) techniques. The surface of an inorganic oxide or an organic polymer then acts as an alternative ligand environment imposing steric and electronic constraints. The so-called heterogenization of homogeneous catalysts is a popular method for the generation of hybrid catalysts, featuring both the advantages of homogeneous and heterogeneous catalysis [235]. Figure 16 shows various types of such supramolecular entities which have been successfully employed in catalytic transformations. Neodymium centers bonded to a carboxylated divinylbenzene crosslinked polystyrene matrix mediate the polymerization of butadiene to *cis*-1,4-polybutadiene in the presence of organoaluminum reagents [236]. Polymer-supported scandium triflate has been employed as a reusable catalyst in several fundamental Lewis acid catalyzed carbon–carbon bond-forming reactions such as aldol, Michael, and Friedel–Crafts acylation reactions [237] and the preparation of diverse quinoline derivatives according to a three-component coupling reaction [238]. Immobilization techniques such as chemisorbed polyacrylonitrile derivatives [PA-Sc-TAD, polyallyl scandium trifylamide ditriflate] and microencapsulated scandium triflate [MC-Sc(OTf)$_3$] have been used. In the latter hybrid system the Sc(III) is probably stabilized by π-interactions with the poly-
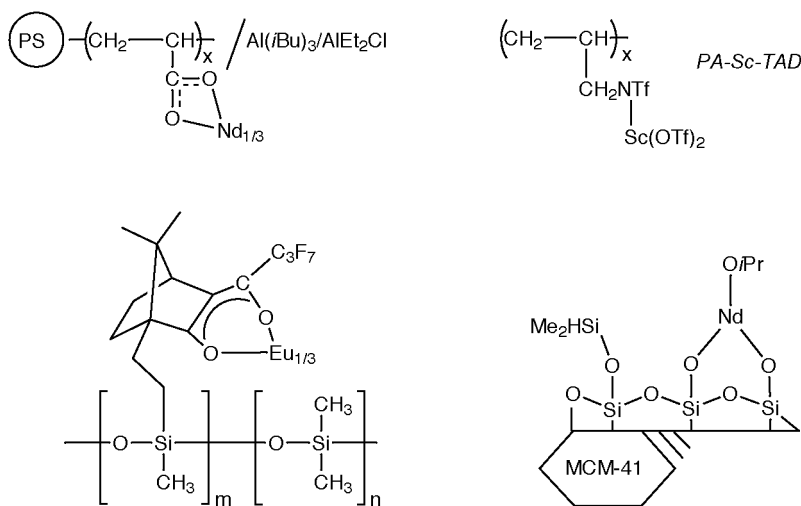

Fig. 16. Heterogenized homogeneous catalysts

styrene backbone. Chiral polysiloxane-fixed europium β-diketonates were found to be reusable catalysts in the Danishefsky hetero-Diels–Alder reaction [239].

Mesoporous silicates of type MCM-41 display versatile, rigid and thermally and chemically robust host materials for the grafting of pseudo-organometallic compounds such as silylamides and alkoxides (Fig. 16) [115,240]. These materials effectively catalyze carbon–carbon bond-forming reactions and functional group transformations, as shown for the Meerwein–Ponndorf–Verley reduction [241]. Heterogeneous reactions of lanthanide metals dissolved in liquid ammonia with free hydroxy groups of silica and alumina [242] or zeolites [243] yielded supported lanthanide species which exhibit catalytic activity in (de-)hydrogenation, isomerization and Michael reactions. Lanthanide amide and imide moieties have been discussed as catalytically active surface species.

5
Reactivity Pattern of Organolanthanide Complexes

The intrinsic properties of the rare earth cations as revealed by their oxophilicity, "hardness", and large size govern the reactivity of organolanthanide complexes. Hence, parallels to the chemistry of aluminum, the group 2 and group 4 elements, and the actinides are often detected. In this section the most important reaction pathways of these highly reactive complexes are surveyed with representative examples. The stoichiometric reactions outlined also represent the elementary steps in catalytic reaction sequences.
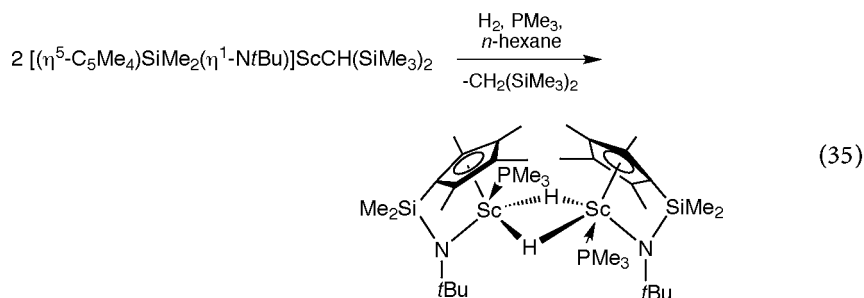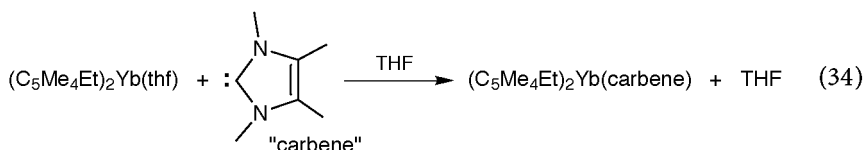
5.1
Donor–Acceptor Interactions

The interaction of the hard, Lewis acidic Ln(III) centers with neutral electron-donating moieties is a ubiquitous feature of organolanthanide complexes. In addition to the electron deficiency of the lanthanide center, steric unsaturation directs this stabilization of the complexes via adduct formation.
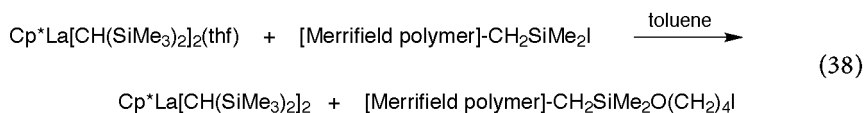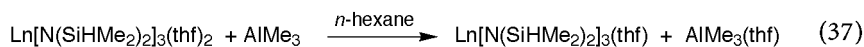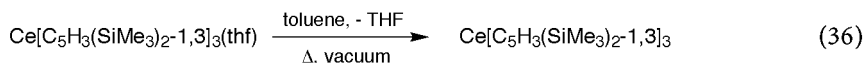
Simple Lewis Acid/Base-Type Interactions
Solvent complexation usually results from salt metathesis reactions which have been carried out in ethereal solvents such as THF or DME. Solvent coordination as a rule decreases the reactivity of Ln–R bonds by depolarization, steric saturation, and competition reactions. On the other hand, donor coordination leads to an enhanced reducing ability of Ln(II) compounds (e.g. HMPA coordination [244]). Lewis base coordination often forces crystallization (e.g. OCPh$_2$, OPPh$_3$, TMEDA) [Eq. (32)] [245,246] and strongly donating ligands such as acetonitrile or pyridine were shown to act as denucleating agents in cyclopentadienyl and alkoxide chemistry [Eq. (33)] [20,247]. Substituted imidazol-2-ylidenes, carbene-type ligands, form strong adduct complexes with Ln(II) and Ln(III) metal centers as indicated by THF displacement [Eq. (34)] [248]. However, coor-
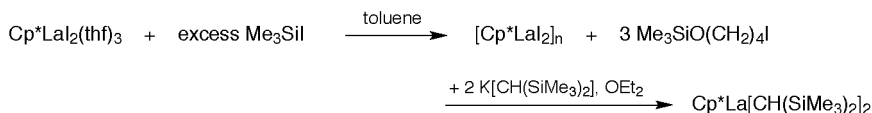
dination of soft Lewis bases was observed in the case of terminally bonded PMe_3 in a highly electrophilic scandium complex [Eq. (35)] [249]. Even water complexes could be trapped as the initial step of the hydrolysis reaction [250]. The vast majority of organic transformations mediated by lanthanide centers depend on pre-coordination of a neutral, functionalized substrate and subsequent formation of an activated species.

$$Ln[N(SiMe_3)_2]_3 \quad + \quad O{=}CPh_2 \xrightarrow{\text{hexane}} Ln[N(SiMe_3)_2]_3(O{=}CPh_2) \tag{32}$$

$$[Dy(OCH\textit{t}Bu)_3]_2 \quad + \quad 4\,CH_3CN \xrightarrow{\text{hexane}} 2\,Dy(OCH\textit{t}Bu)_3(CH_3CN)_2 \tag{33}$$

$$(C_5Me_4Et)_2Yb(thf) \quad + \quad \text{:} \overset{\text{"carbene"}}{\Big\langle} \xrightarrow{\text{THF}} (C_5Me_4Et)_2Yb(carbene) \quad + \quad THF \tag{34}$$

$$2\,[(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}N\textit{t}Bu)]ScCH(SiMe_3)_2 \xrightarrow[\text{-}CH_2(SiMe_3)_2]{\overset{H_2,\,PMe_3,}{\overset{n\text{-hexane}}{}}}$$
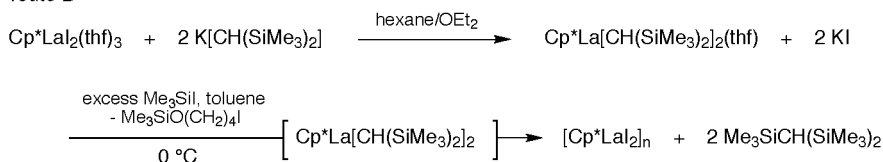

$$\tag{35}$$

The reverse process, desolvation, is often more difficult to achieve. Thermal treatment (*toluene method*) [Eq. (36)] [251], intermetallic Lewis acid/base competition reactions [Eq. (37)] [252,253], and $SiMe_3I$-mediated ring opening [Eq. (38)] [254] have been applied for THF removal. The two latter variants have been probed both homogeneously and heterogeneously. Depending on the desolvating reagent, donor solvent removal is favorably accomplished at an early stage of a multistep synthesis (Scheme 14) [254].

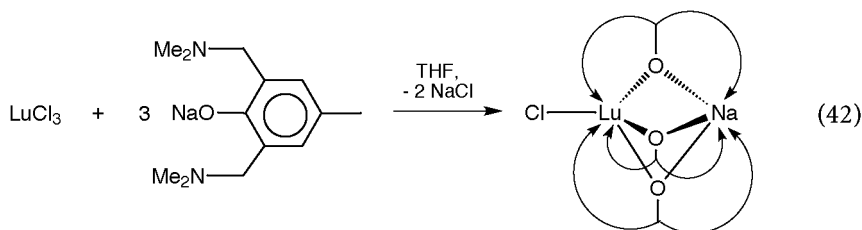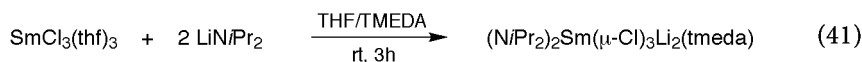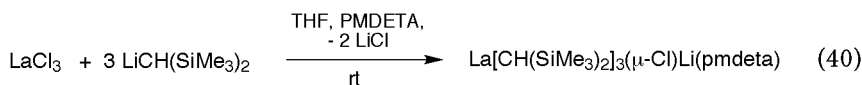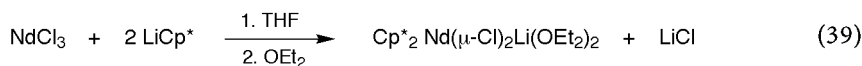$$Ce[C_5H_3(SiMe_3)_2\text{-}1,3]_3(thf) \xrightarrow[\Delta,\,\text{vacuum}]{\text{toluene, - THF}} Ce[C_5H_3(SiMe_3)_2\text{-}1,3]_3 \tag{36}$$

$$Ln[N(SiHMe_2)_2]_3(thf)_2 + AlMe_3 \xrightarrow{n\text{-hexane}} Ln[N(SiHMe_2)_2]_3(thf) + AlMe_3(thf) \tag{37}$$

$$Cp^*La[CH(SiMe_3)_2]_2(thf) \quad + \quad [\text{Merrifield polymer}]\text{-}CH_2SiMe_2I \xrightarrow{\text{toluene}}$$

$$\tag{38}$$

$$Cp^*La[CH(SiMe_3)_2]_2 \quad + \quad [\text{Merrifield polymer}]\text{-}CH_2SiMe_2O(CH_2)_4I$$

route A

$$\text{Cp*LaI}_2(\text{thf})_3 \quad + \quad \text{excess Me}_3\text{SiI} \xrightarrow{\text{toluene}} [\text{Cp*LaI}_2]_n \quad + \quad 3\ \text{Me}_3\text{SiO(CH}_2)_4\text{I}$$

$$\xrightarrow[\ ]{+\ 2\ \text{K[CH(SiMe}_3)_2], \text{ OEt}_2} \text{Cp*La[CH(SiMe}_3)_2]_2$$

route B

$$\text{Cp*LaI}_2(\text{thf})_3 \quad + \quad 2\ \text{K[CH(SiMe}_3)_2] \xrightarrow{\text{hexane/OEt}_2} \text{Cp*La[CH(SiMe}_3)_2]_2(\text{thf}) \quad + \quad 2\ \text{KI}$$

$$\xrightarrow[0\ °C]{\substack{\text{excess Me}_3\text{SiI, toluene} \\ -\ \text{Me}_3\text{SiO(CH}_2)_4\text{I}}} \left[\ \text{Cp*La[CH(SiMe}_3)_2]_2\ \right] \longmapsto [\text{Cp*LaI}_2]_n \quad + \quad 2\ \text{Me}_3\text{SiCH(SiMe}_3)_2$$

Scheme 14. Solvent-free rare earth alkyl species – THF removal at an early stage

Ate Complexation

The formation of anionic rare earth metal ligand moieties or ate complexation are commonly observed features of salt metathesis reactions when alkali metal cyclopentadienyl [147], alkyl [96], amide [97,255] and alkoxide derivatives are employed [Eqs. (39)-(42)] [256].

$$\text{NdCl}_3 \quad + \quad 2\ \text{LiCp*} \xrightarrow[\text{2. OEt}_2]{\text{1. THF}} \text{Cp*}_2\,\text{Nd}(\mu\text{-Cl})_2\text{Li(OEt}_2)_2 \quad + \quad \text{LiCl} \qquad (39)$$

$$\text{LaCl}_3 \quad + \quad 3\ \text{LiCH(SiMe}_3)_2 \xrightarrow[\text{rt}]{\substack{\text{THF, PMDETA,} \\ -\ 2\ \text{LiCl}}} \text{La[CH(SiMe}_3)_2]_3(\mu\text{-Cl})\text{Li(pmdeta)} \qquad (40)$$

$$\text{SmCl}_3(\text{thf})_3 \quad + \quad 2\ \text{LiN}i\text{Pr}_2 \xrightarrow[\text{rt, 3h}]{\text{THF/TMEDA}} (\text{N}i\text{Pr}_2)_2\text{Sm}(\mu\text{-Cl})_3\text{Li}_2(\text{tmeda}) \qquad (41)$$

$$\text{LuCl}_3 \quad + \quad 3\ \text{NaO} \cdots \xrightarrow[]{\substack{\text{THF,} \\ -\ 2\ \text{NaCl}}} \qquad (42)$$

Ate complexation, as main product or as contamination, occurs via coordination of additional counter ligands or alkali metal halide incorporation. The removal of alkali metal halides can often only be achieved by tedious extraction experiments [257] or in the case of thermally stable compounds via sublimation [258]. Due to the additional electronic and steric saturation of the metal environment, the reactivity of ate complexes is significantly decreased. Ate complexation can be
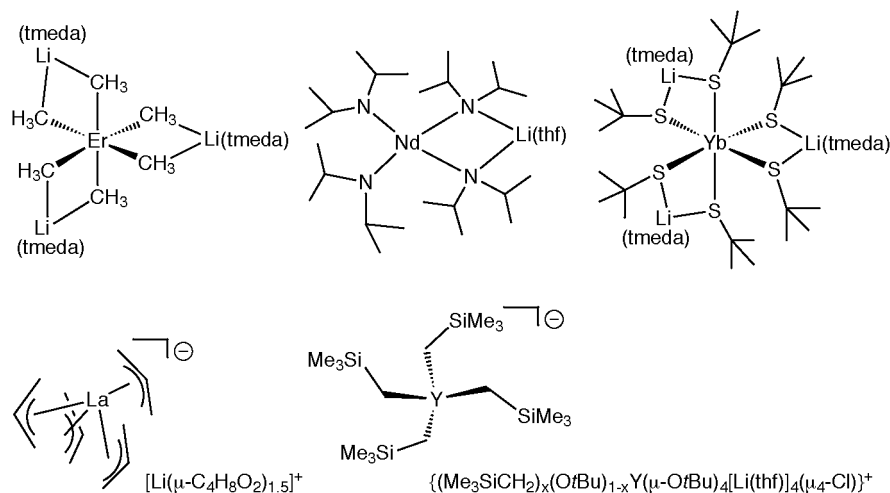
Fig. 17. Stabilization of reactive homoleptic complexes via ate complexation

avoided by the application of alternative synthetic procedures such as the *silyl-amide* route (Sect. 3.3). Although ate complexation is considered a nuisance for the preparation of highly reactive lanthanide species, promising synthetic and catalytic behavior has been ascribed. For example, ligand exchange reactions involving heterobimetallic ate systems can proceed via retention of the metal composition [125]. Their potential for cation exchange reactions still has to be examined. Rare earth binolate complexes of the type $Na_3La[(S)-BINOL]_3(thf)_6(H_2O)$ effectively catalyze enantioselective carbon–carbon bond-forming reactions [43] and heterobimetallic complexes containing linked amido-cyclopentadienyl ligands, $Li[Ln(\eta^5:\eta^1-C_5Me_4SiMe_2NCH_2CH_2NMe_2)_2]$, have been reported to be active in the ring-opening polymerization of lactones and lactides [219].

The stabilization of otherwise labile homoleptic complexes is another useful option of ate complexation. This can occur via ion pair formation [174,259] or entrapment of the cationic moieties in the ligand sphere (Fig. 17) [120,184,260].

Neutral π-Donor Ligation – Arene and Olefin Coordination

The coordination of an alkene to an electron-deficient metal center is the proposed preceding step to the insertion into Ln–C, Ln–H and Ln–N bonds [22,145]. η^2-Olefin and alkyne complexes of the lanthanide elements are particularly unstable due to the lack of $d\pi$-$p\pi$ back-bonding to the coordinated alkene [261–268]. However, tailoring of the olefin environment by maximization of the Lewis basicity of the alkene [262] or utilizing chelation effects [263] has led to complexes indentified by structure analysis and NMR spectroscopy, respectively (Fig. 18). η^6-Arene coordination is considerably more stable than η^2-olefin coordination and can occur in a mono(arene) [265], bis(arene) (Sect. 3.2) [26] and intermolecular fashion [247]. Lanthanide π-donor ligation is observed in the ab-
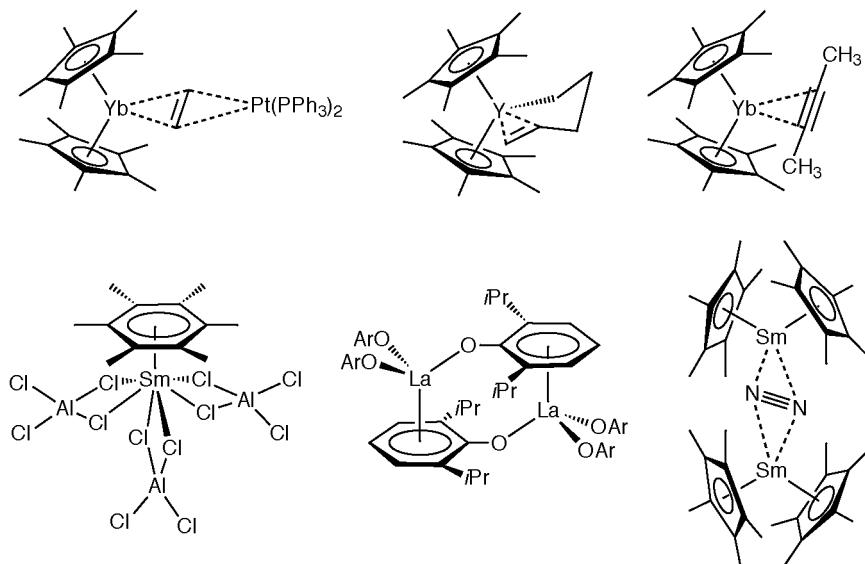
Fig. 18. π-Donor interactions in organolanthanide chemistry

sence of coordinating solvent molecules only. Pseudo-η^2-π-bonded complexes involving hydrogen [266] and nitrogen [267] also show reversible coordination with Ln(II) fragments. In contrast, the reaction of SmCp*$_2$ with hydrazine produces a dinuclear Sm(III) complex featuring a bridging (NHNH)$^{2-}$ moiety [268].

Agostic Interactions

The term "agostic" bonding, originally proposed for the formation of two-electron three-center bonds of the type C–H→M [269], is now often used in lanthanide chemistry to describe the interaction of a highly electron-deficient, sterically unsaturated metal center with "CH", "SiMe", and "SiH" ligand fragments. These intramolecular, chelate-type interactions are of predominantly electrostatic nature (Fig. 19) [270]. Although the agostic bonding is weak and usually not observed in solution [271], it can have significant implications for the molecular and electronic structure and hence reactivity of the molecule. The solid state structures often reveal quite remarkable angle distortions within the agostically interacting fragment. Detailed studies performed on complexes which are active in olefin polymerization propose that α-C-H agostic interactions assist chain propagation (transition state) [272], while β-C-H interactions retard ethylene insertion (ground state) [273]. Strong β-Si-H diagostic interactions can be formed even in the presence of a coordinating solvent. Such potentially tridentate chelating arrays direct the *rac/meso* ratio in *ansa*-lanthanidocene complexes [117]. The intramolecular agostic approach is routinely observed in electron-deficient complexes of the bulky ligand CH(SiMe$_3$)$_2$ [274]. The presence of a
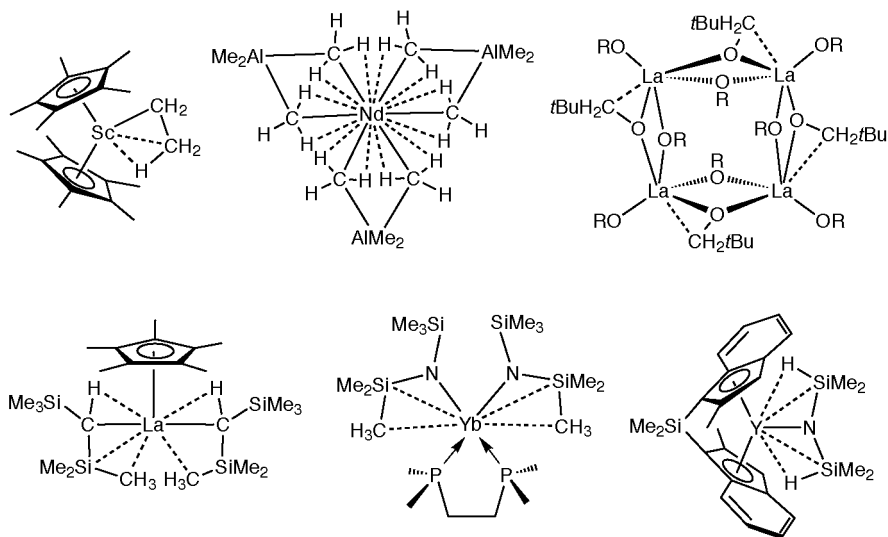
Fig. 19. Agostic interactions in organolanthanide chemistry

multi-agostic interaction was proposed in permethylated complexes $Ln(AlMe_4)_3$, yielding formal coordination numbers as high as 18 [275]. The formation of agostic interactions is not restricted to compounds containing metal–carbon bonds, as evidenced by the ring structure of $[La(OCH_2tBu)_3]_4$ [276]. Bulky amide and aryloxide (sulfide) ligands such as $N(SiMe_3)_2$ [277], $N(SiHMe_2)_2$ [117], and $NiPr_2$ [120] offer another agostic reservoir as emphasized in the important synthetic precursors $Ln[N(SiMe_3)_2]_3$ [114] and $Ln(OC_6H_3tBu_2\text{-}2,6)_3$ [101].

5.2
Complex Agglomerization

Steric and electronic factors often force the stabilization of monometallic species via agglomerization. As a rule, the formation of di- and multinuclear species is achieved by intermolecular bridging of the smallest, most reactive and labile Ln–X bond and, hence, leads to decreased reactivity.

Dinuclear Complexes
The formation of dinuclear complexes is routinely observed along with the important class of lanthanidocene complexes of type Cp_2LnR when R is a sterically less demanding ligand such as H, Me or a small alkoxide group [4]. Depending on the metal and ligand size, bridging can also occur in an asymmetric fashion as evidenced in $[Cp^*_2Lu(CH_3)]_2$ [Eq. (43)] [145]. The formation of dinuclear ligand bridged species is also observed in organo-Ln(II) chemistry. Two representative examples are given in Eqs. (44) und (45) [127,278]. Rare earth amide and

alkoxide complexes show an even more pronounced tendency of agglomerization [Eq. (46)] [159].

$$Cp^*_2Lu(\mu\text{-}CH_3)_2AlMe_2 \xrightarrow[\text{2. NEt}_3, \text{ vacuum}]{\substack{\text{1. OEt}_2, \text{ - AlMe}_3(\text{OEt}_2) \\ \text{-40°C}}} Cp^*_2Lu\overset{CH_3}{\underset{CH_3}{\cdots\cdots}}LuCp^*_2 \qquad (43)$$

$$2\,SmI_2(thf)_2 \; + \; 2\,KCp^* \xrightarrow{\text{THF}} (thf)_2Cp^*Sm\overset{I}{\underset{I}{\cdots\cdots}}SmCp^*(thf)_2 \qquad (44)$$

$$\{Yb[N(SiMe_3)_2]_2\}_2 \xrightarrow[\text{rt, 16h}]{\substack{\text{+ 2 HOC}t\text{Bu}_3, \\ \text{hexane,} \\ \text{- 2 HN(SiMe}_3)_2}} (Me_3Si)_2N{-}Yb\overset{Ct\text{Bu}_3}{\underset{Bu_3Ct}{\overset{O}{\underset{O}{\cdots\cdots}}}}Yb{-}N(SiMe_3)_2 \qquad (45)$$

$$2\,Lu[N(SiMe_3)_2]_3 \; + \; 6\,HOCMe_2CH_2OMe \xrightarrow[\text{rt, 16h}]{\substack{n\text{-hexane,} \\ \text{- 6 HN(SiMe}_3)_2}} \qquad (46)$$

$$(\eta^2\text{-OR})Lu(\mu,\eta^2\text{-OR})_3Lu(\eta^1\text{-OR})_2$$
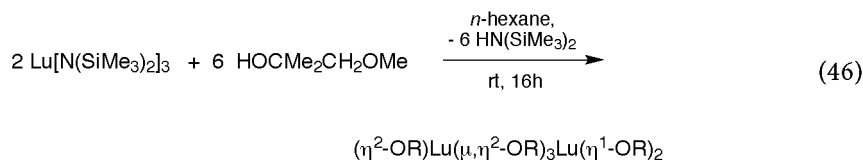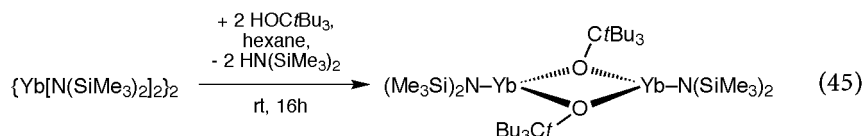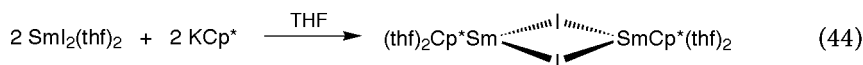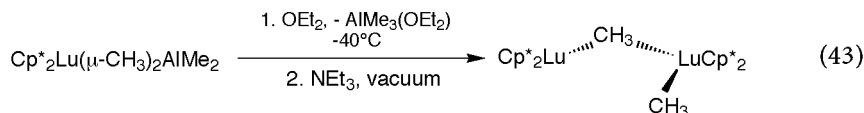
Self Assembly – Rings and Clusters

In the absence of strongly coordinating donor molecules, specific ligand arrangements can direct the formation of higher agglomerated systems (Fig. 20). Depending on the Ln/Cp ratio, the formation of rings (Cp/Ln=2) and clusters (Cp/Ln<2) can be observed in cyclopentadienyl (pseudo-)halide complexes [279]. $[Cp^*_2Sm(\mu\text{-CN})]_6$ obtained by a thermal hetero-ligand degradation reaction involving $N(SiMe_3)CH(Ph)(N=CHPh)$ is composed of a 18-membered ring, exhibiting a S_6-symmetric chair conformation [280]. In the presence of coordinating isonitrile ligands $[Cp^*_2Sm(\mu\text{-CN})(CNc\text{-}C_6H_{11})]$ is formed featuring a 9-membered ring [281]. Lower Cp/Ln ratios inevitably create further coordination sites at the metal center and lead to cluster formation. $[Cp^*_6Yb(\mu\text{-F})_4]$ (Cp/Ln= 1.2) is a rare example of a ring-cluster hybrid molecule [282]. A highly symmetric icosaeder arrangement of the metal centers was observed in $[Cp_{12}Sm_{12}(\mu\text{-Cl})_{24}]$ (Cp/Ln=1) containing a centered Cl_4 tetrahedron [283]. Ring formation is less predictable in alkoxide chemistry, as revealed by the decameric constitution of $[Y(OCH_2CH_2OMe)_3]_{10}$ [284]. In the presence of small charge densities such as Cl, OH, and O alkoxide, cluster formation is the preferred agglomerization pathway [285]. A few cluster compounds featuring only amide ligands have been reported [97].
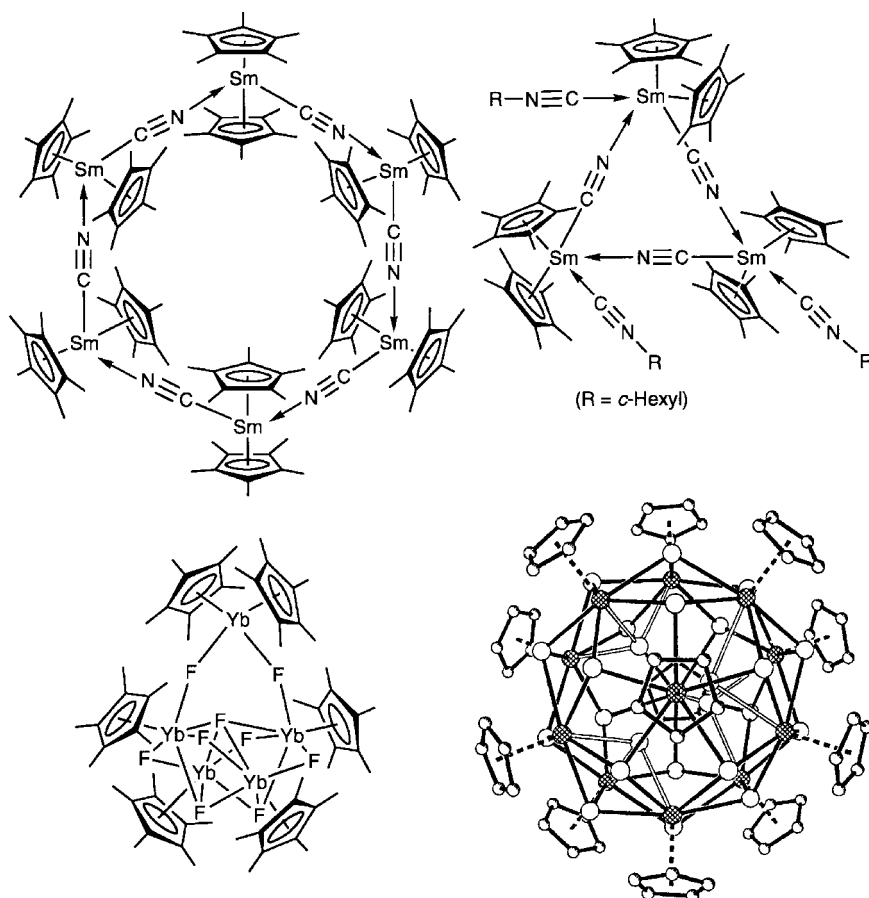
**Fig. 20.** Self assembly of cyclopentadienyl derivatives – rings and clusters

5.3
## Ligand Exchange and Redistribution Reactions

The vast majority of ligand exchange reactions such as salt metathesis, amine elimination, and hydrogenolysis have already been addressed to in the previous sections. The high ligand exchange ability is a peculiar feature of lanthanide complexes and of fundamental importance for their catalytic application. Even the thermodynamically very strong lanthanide alkoxide and amide bonds are kinetically labile as found in transamination and transalcoholysis reactions [158]. Donor ligand exchange as a rule occurs via dissociation processes and the exchange rate of water has been studied in detail in the context of biologically and medically relevant processes [286]. Counter ligand exchange proceeds via
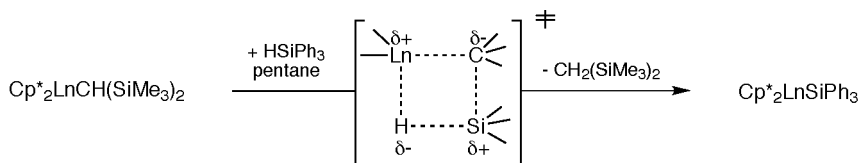
Scheme 15. Ln-C/Si-H transposition in the σ-bond metathesis reaction
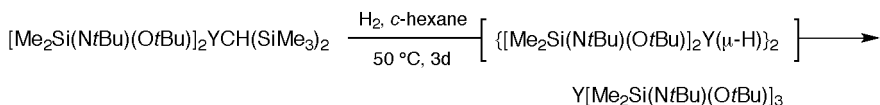
Scheme 16. Ligand redistribution (disproportionation) in a heteroleptic alkyl complex
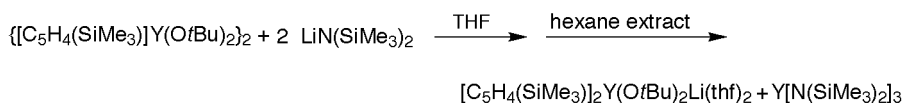
Scheme 17. Ligand redistribution in a heteroleptic cyclopentadienyl complex

σ-bond metathesis involving four-centered transition states. Such converted processes are often the proposed key intermediates (turnover-limiting steps) in hydrogenolysis reactions, and are shown in Scheme 15 for the Si-H/Ln-C transposition of the catalytic hydrosilylation reaction [144]. The pronounced electrophilicity of the lanthanide centers mediates the activation of C–H bonds of a range of hydrocarbons including methane [Eq. (47)] [287]. C-H activation of propene by organolanthanide hydride systems leads to allyl complexes, an important deactivation step in organolanthanide-catalyzed propene polymerization [Eq. (48)] [147,288]. Thermal treatment of $Cp^*_2LaCH(SiMe_3)_2$ led to agglomerization via intramolecular C-H activation [Eq. (49)] (cf. Sect. 5.5) [289].
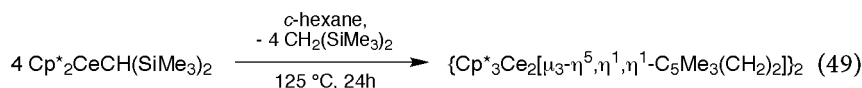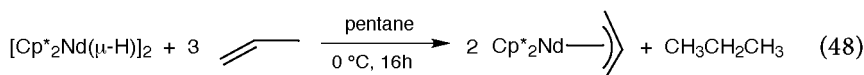
Ligand redistribution (scrambling, disproportionation) can occur in heteroleptic compounds, the formation of the most stable homoleptic derivatives being the driving force [Schemes 16 and 17, Eq. (50)] [139,215,290].

$$1.5 \{Eu[N(SiMe_3)_2]_2(\mu\text{-Cl})(thf)\}_2 \xrightarrow{\text{toluene}} 2 \, Eu[N(SiMe_3)_2]_3 \; + \; EuCl_3(thf)_x \qquad (50)$$
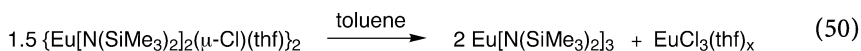
5.4
Insertion Reactions

The formal insertion of double and triple bonds into reactive Ln–H, Ln–C, and Ln–N bonds is of fundamental significance in a large number of catalytic reactions. Direct insertion of olefins such as propene into a Lu–Me bond has been detected as part of the "lanthanide model for Ziegler–Natta polymerization" [Eq. (51)] [291]. Alkene and alkyne insertion is also a key step in the hydroamination/cyclization reaction of *N*-unprotected aminoolefins [292]. Insertion of polarized double bonds such as carbon monoxide and acetonitrile often leads to highly functionalized reaction products. Carbon monoxide insertion into lanthanide alkyl bonds can occur in a single and multiple fashion with the formation of η^2-acyl and enedione diolate moieties, respectively (Scheme 18) [293]. The insertion of the metal-bonded carbonyl of CpCo(CO)$_2$ into a Sc–Me bond led to a heterobimetallic system [Eq. (52)] [294]. A non-classical carbocation species was isolated from the insertion of CO into one cyclopentadienyl moiety of the sterically crowded complex SmCp*$_3$ [Eq. (53)] [295]. This is a remarkable reaction promoted by steric constraints. A "Sc-Si(SiMe$_3$)$_3$" moiety mediates the insertion and coupling of the isocyanide CN(Xyl) (Scheme 19) [296]. The subsequent rapid intramolecular rearrangement reactions probably proceed via a reactive silene intermediate.

(51)

(52)

(53)
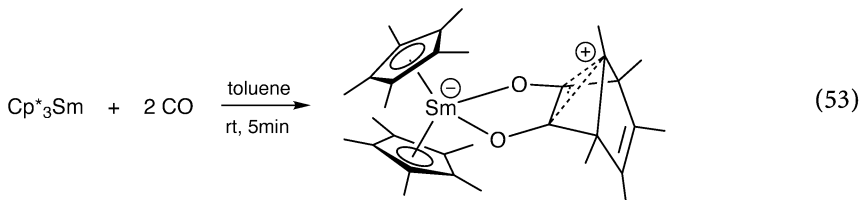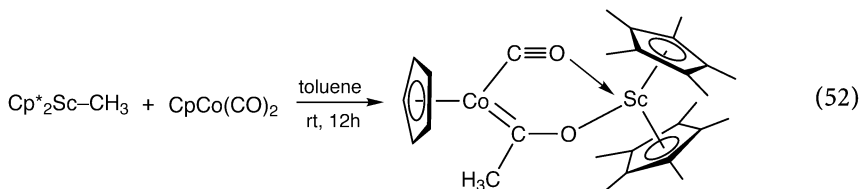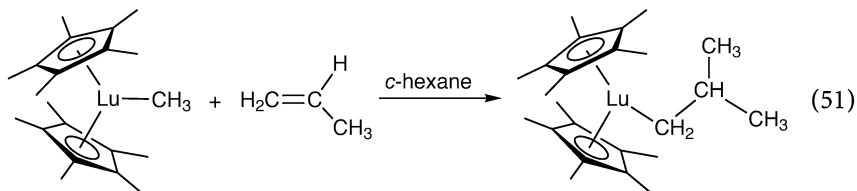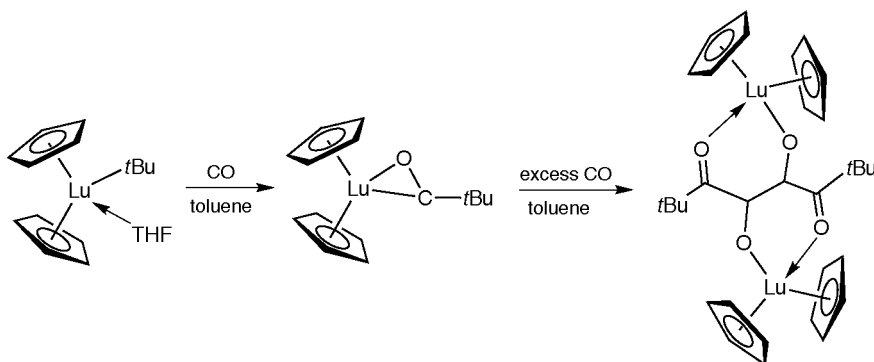
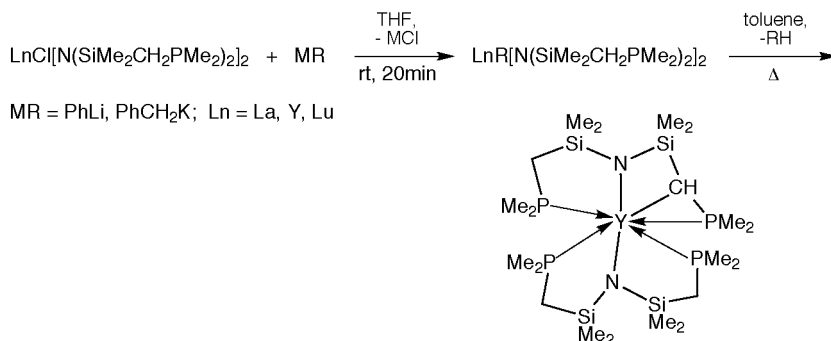**Scheme 18.** Single and multiple carbon monoxide insertion into a lutetium alkyl bond
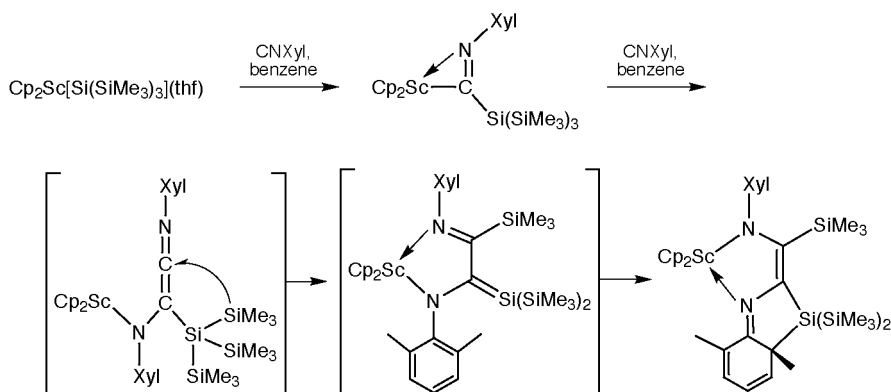
Scheme 19. Double insertion of CN(Xyl) into a scandium silicon bond (Xyl=$C_6H_3Me_2$-2,6)

5.5
Elimination Reactions – Ligand Degradation
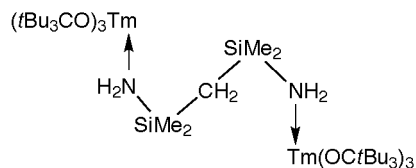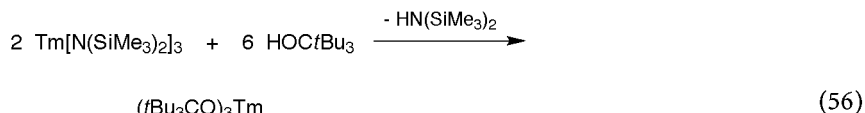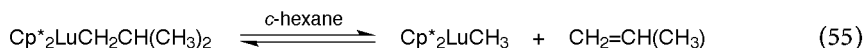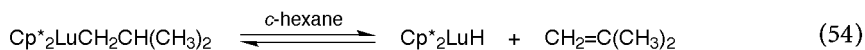
β-H and β-alkyl elimination have been reported as major decomposition routes of lanthanide alkyl bonds. These extrusion reactions were initially observed in Cp^*_2Ln-R catalysts and can be considered as models for chain termination oc-curing during propene polymerization [Eqs. (54) and (55)] [297]. The intramo-lecular ligand metallation and concomitant hydrocarbon extrusion found in amide templated complexes depend on the metal size and alkyl ligand (Scheme 20) [298]. Silylamine fragmentation has been observed along with the synthesis of the alkoxide complexe $Tm(OCtBu_3)_3$ according to the silylamide route [Eq. (56)] [114]. In corresponding exchange reactions with excess of fluor-inated alcohols HOR^F, ammonia is the final degradation product of the si-

$$LnCl[N(SiMe_2CH_2PMe_2)_2]_2 \;+\; MR \xrightarrow[\text{rt, 20min}]{\text{THF,} \atop -\text{MCl}} LnR[N(SiMe_2CH_2PMe_2)_2]_2 \xrightarrow[\Delta]{\text{toluene,} \atop -\text{RH}}$$

MR = PhLi, PhCH$_2$K; Ln = La, Y, Lu

Scheme 20. Thermally induced intramolecular alkane (benzene) elimination

lylamine, trapped as an ammine complex. The bulkiness and the basicity of the alkoxide ligand, and the type of solvent, effect the ammonia formation [299]. Due to its relevance to the conversion of oxofunctionalized substrates the unexpected cleavage of acetylacetone in the presence of an yttrium alkoxide is shown in Eq. (57) [300].
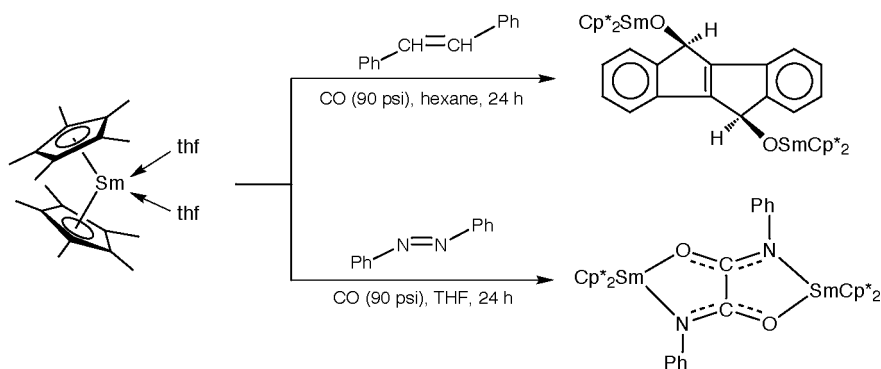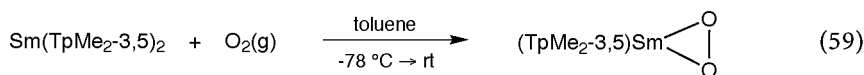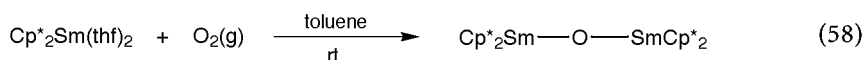
$$Cp^*_2LuCH_2CH(CH_3)_2 \xrightleftharpoons{\text{c-hexane}} Cp^*_2LuH \;+\; CH_2=C(CH_3)_2 \qquad (54)$$

$$Cp^*_2LuCH_2CH(CH_3)_2 \xrightleftharpoons{\text{c-hexane}} Cp^*_2LuCH_3 \;+\; CH_2=CH(CH_3) \qquad (55)$$

$$2\ Tm[N(SiMe_3)_2]_3 \;+\; 6\ HOCtBu_3 \xrightarrow{-\ HN(SiMe_3)_2}$$

(56)

$$Y_5O(OiPr)_{13} \;+\; \text{excess Hacac} \xrightarrow[\text{20 °C, 24 h}]{\text{toluene}}$$

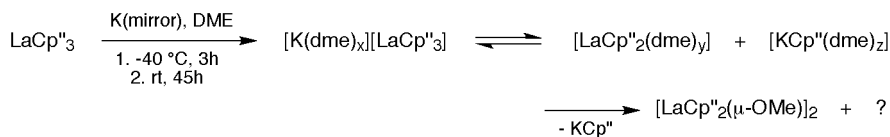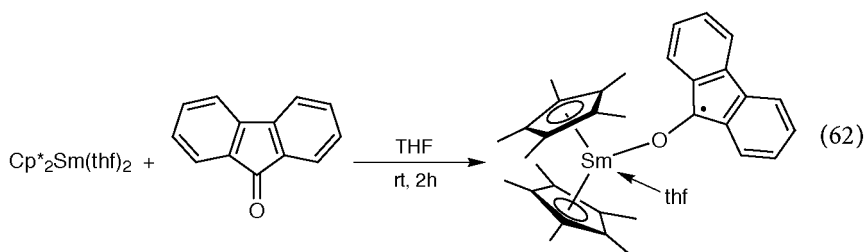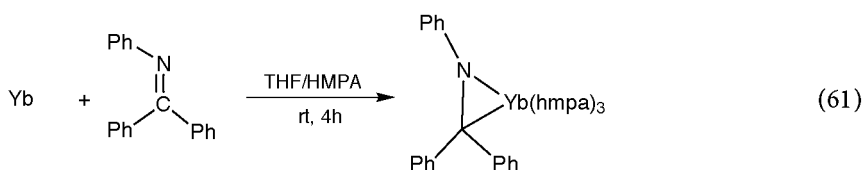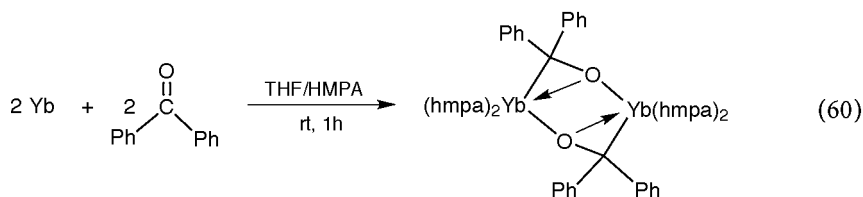(57)
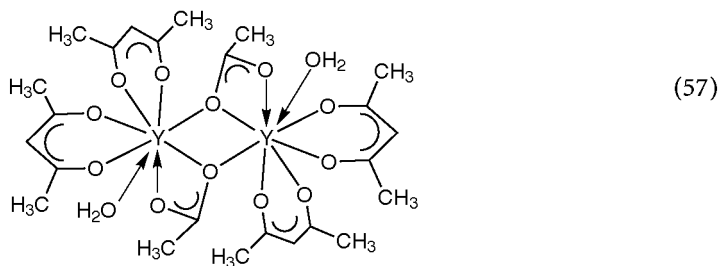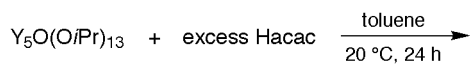
5.6
Redox Chemistry

Kagan and co-workers pioneered the work on the reductive behavior of the low oxidation states of the lanthanide elements in organic synthesis [2b]. Ln metals and Ln(II) derivatives were subsequently found to promote a number of important individual reactions [301]. "The combination of one- and two-electron chemistry sets SmI_2 apart from virtually every other reductive coupling agent currently available" and exhibits exceptional properties for sequential conversions tolerating unprotected functional groups [1b].

Evans and co-workers have worked out the peculiar reducing ability of Sm(II) with the corresponding organometallic reagents, in particular $Cp*_2Sm(thf)_x$, and characterized many metal-bonded products by X-ray crystallography [32]. Their standard reagent is readily oxidized by oxygen to form an oxo-bridged dimer [Eq. (58)] [302]. In contrast, the tris(3,5-dimethylpyrazole)hydroborate ligand produces a superoxo complex under an atmosphere of oxygen [Eq. (59)] [303]. Again, steric and electronic constraints at the metal center, induced by the ligand environment, seem to force this different reaction behavior. Examples of the unique reductive potential of $Cp*_2Sm$ include the functionalization of unsaturated hydrocarbon substrates with carbon monoxide (Scheme 21) [304,305].
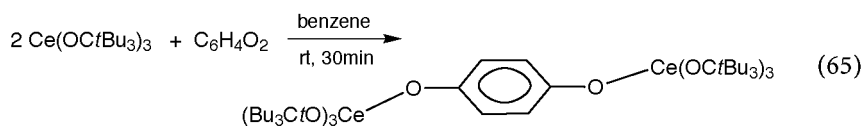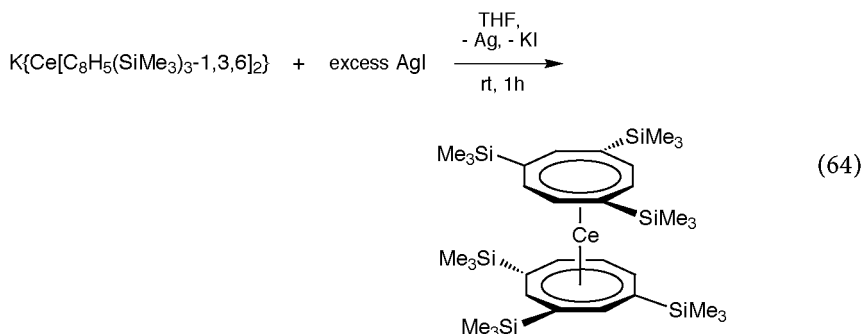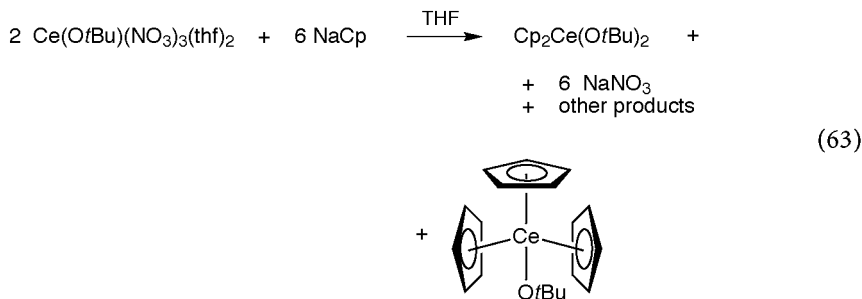
$$Cp*_2Sm(thf)_2 \ + \ O_2(g) \ \xrightarrow[\text{rt}]{\text{toluene}} \ Cp*_2Sm\!\!-\!\!O\!\!-\!\!SmCp*_2 \qquad (58)$$

$$Sm(TpMe_2\text{-}3,5)_2 \ + \ O_2(g) \ \xrightarrow[\text{-78 °C} \rightarrow \text{rt}]{\text{toluene}} \ (TpMe_2\text{-}3,5)Sm\!\!<\!\!\begin{smallmatrix}O\\|\\O\end{smallmatrix} \qquad (59)$$

Scheme 21. The reductive potential of $Cp*_2Sm(thf)_2$

The reaction of one-electron reducing agents with ketones yields radical anions (ketyls) which are key intermediates in a variety of carbonyl group transformations. Reduction of aromatic ketones by low-valent samarium and ytterbium compounds [Ln metal and Ln(II)] allowed the first trapping of these radicals in the coordination sphere of a metal [306]. The isolation of an Yb(II) benzophenone dianion [Eq. (60)] [307], a lanthanoid-imine azametallacyclopropane complex [Eq. (61)] [308], and a heteroleptic fluorenone ketyl organosamarium(III) complex [Eq. (62)] [309] by Hou and co-workers emphasize the usefulness of hexamethylphosphoramide (HMPA) and sterically demanding groups as stabilizing ligands. The reaction of $La[\eta^5\text{-}C_5H_3(SiMe_3)_2\text{-}1,3]$ with a potassium mirror in dimethoxyethane produced a lanthanocene(III) methoxide complex via persistent paramagnetic La(II) intermediates (Scheme 22) [310].

$$2\ Yb\ +\ 2\ \underset{Ph}{\overset{O}{\underset{|}{\overset{||}{C}}}}\ Ph\ \xrightarrow[\text{rt, 1h}]{\text{THF/HMPA}}\ (hmpa)_2Yb\underset{O}{\overset{O}{<}}Yb(hmpa)_2 \qquad (60)$$

$$Yb\ +\ \underset{Ph}{\overset{Ph\diagdown N}{\underset{|}{\overset{||}{C}}}}\ Ph\ \xrightarrow[\text{rt, 4h}]{\text{THF/HMPA}}\ \qquad (61)$$

$$Cp^*{}_2Sm(thf)_2\ +\ \xrightarrow[\text{rt, 2h}]{\text{THF}}\ \qquad (62)$$

$$LaCp''_3\ \xrightarrow[\substack{\text{1. -40 °C, 3h}\\ \text{2. rt, 45h}}]{\text{K(mirror), DME}}\ [K(dme)_x][LaCp''_3]\ \rightleftharpoons\ [LaCp''_2(dme)_y]\ +\ [KCp''(dme)_z]$$

$$\xrightarrow[-\ KCp'']{}\ [LaCp''_2(\mu\text{-OMe})]_2\ +\ ?$$

Scheme 22. Generation of low-valent lanthanum reaction intermediates $[Cp''=C_5H_3(SiMe_3)_2\text{-}1,3]$

Only a few complexes containing Ce(IV)–carbon bonds have been structurally characterized so far. Salt metathesis reactions utilizing mixed alkoxide nitrate Ce(IV) precursors [Eq. (63)] [311], as well as the oxidative salt elimination of K[Ce(COT)]$_2$ ate complexes with silver iodide, led to isolable organocerium(IV) species [Eq. (64)] [80e]. The oxidation of the homoleptic Ce(III) alkoxide Ce(OCtBu$_3$)$_3$ with benzoquinone yielded a dinuclear heteroleptic Ce(IV) complex [Eq. (65)] [312].

$$2 \; Ce(OtBu)(NO_3)_3(thf)_2 \; + \; 6 \; NaCp \; \xrightarrow{THF} \; Cp_2Ce(OtBu)_2 \; +$$

$$+ \; 6 \; NaNO_3$$
$$+ \; other \; products$$

(63)

$$K\{Ce[C_8H_5(SiMe_3)_3\text{-}1,3,6]_2\} \; + \; excess \; AgI \; \xrightarrow[rt, \, 1h]{THF, \\ - Ag, - KI}$$

(64)

$$2 \; Ce(OCtBu_3)_3 \; + \; C_6H_4O_2 \; \xrightarrow[rt, \, 30min]{benzene}$$

(65)

5.7
Reaction Sequences – Catalytic Cycles

The vast majority of the reaction pathways outlined in the preceding sections can be rediscovered as basic steps in many organolanthanide-mediated organic transformations. The well-examined mechanistic scenarios shown as follows
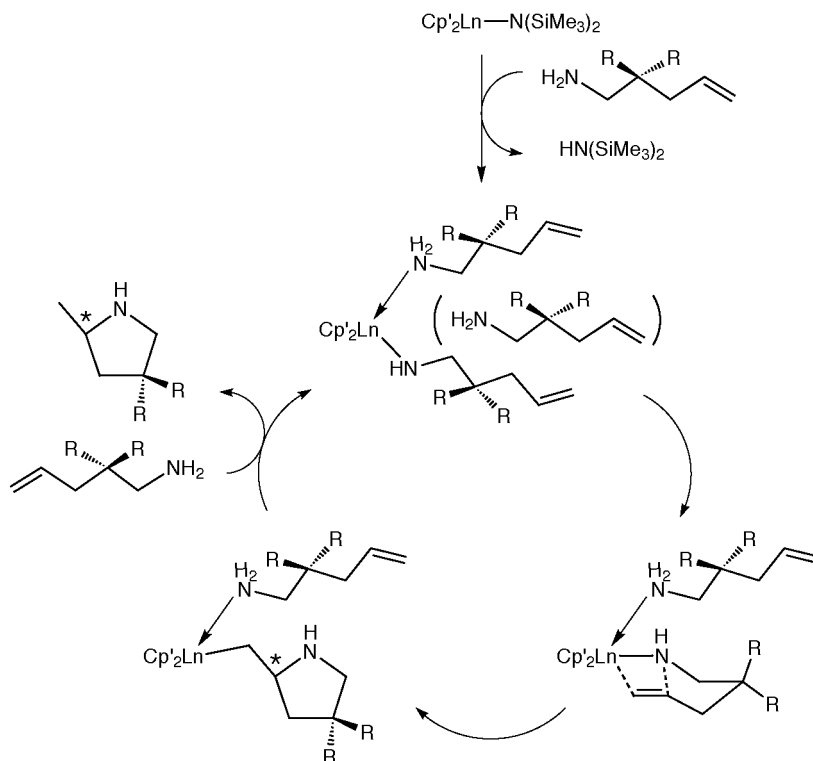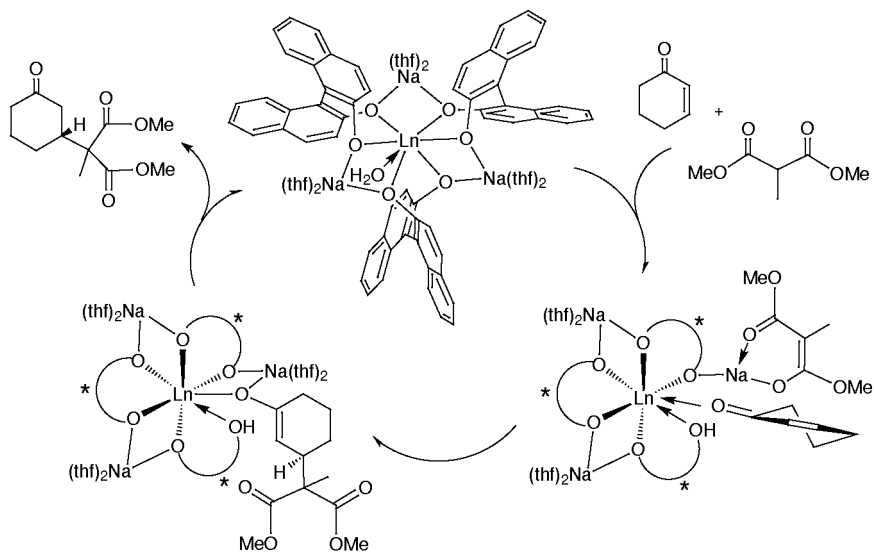
Scheme 23. Organolanthanide-catalyzed hydroamination

with the hydroamination (Scheme 23) [218a,292], Michael addition (Scheme 24) [313], and MMA polymerization reactions (Schemes 25 and 26) [314,315] summarize this section.

5.8
Side Reactions

The intrinsic properties and concomitant high reactivity of organolanthanide moieties often lead to unforeseen and undesired products under the prevailing reaction and storage conditions and, finally, some of these cause accidental reactions such as ether cleavage [Eqs. (66)–(68)] [94, 177,316–318], carbon dioxide insertion [Eq. (69)] [319], or partial hydrolysis [Eq. (70)] [320]. Cluster formation [285] of complexes containing small alkoxide ligands is often observed in the presence of traces of water and proceeds via hydrolysis/dehydration/dealkoxylation processes [Eq. (71)] [321]. In these systems the oxo and hydroxo moieties occupy central cluster positions where they can accomplish high metal coordination (CN=6).
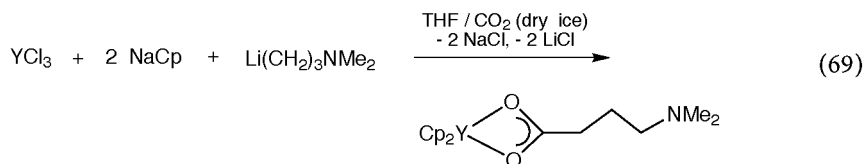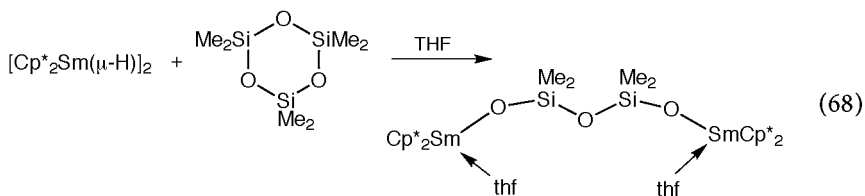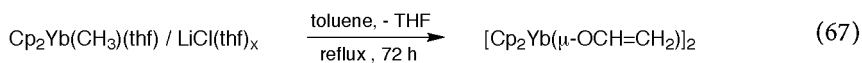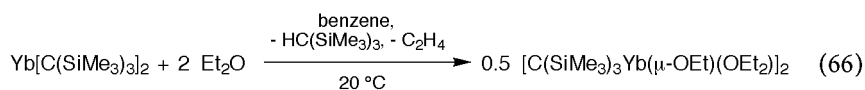
Scheme 24. Heterobimetallic multifunctional catalysis of a Michael reaction by Na$_3$[La(S)-BINOL]$_3$(thf)$_6$(H$_2$O)
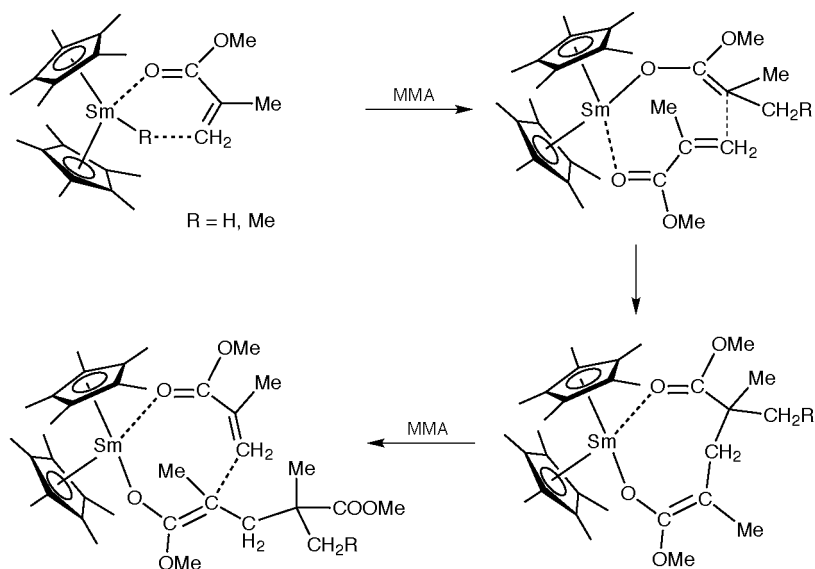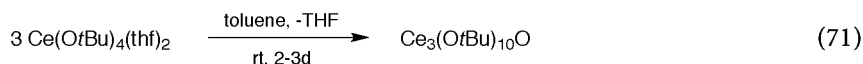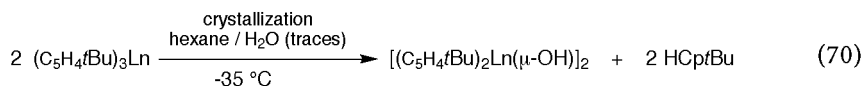

Scheme 25. Organolanthanide(III)-catalyzed methylmethacrylate polymerization
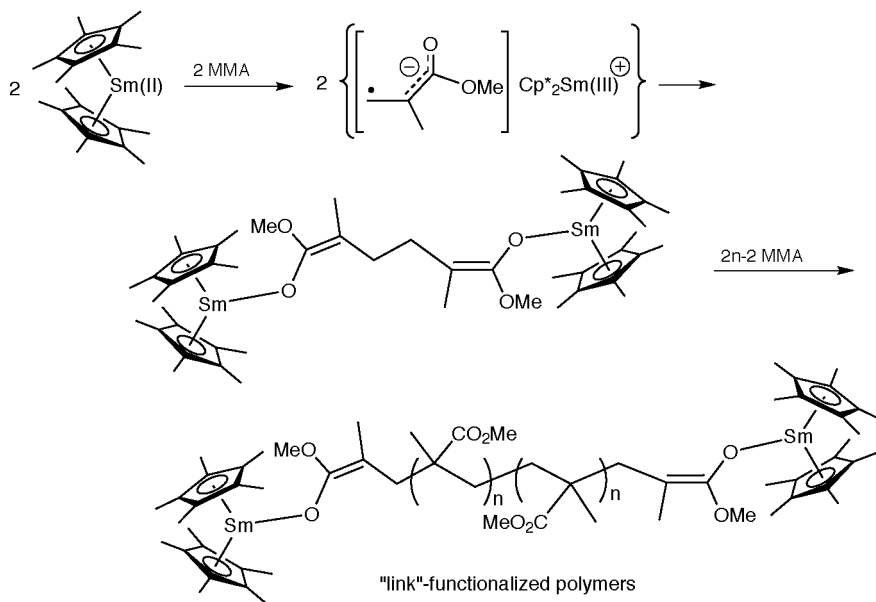
Scheme 26. Organosamarium(II)-initiated methylmethacrylate polymerization

$$Yb[C(SiMe_3)_3]_2 + 2\ Et_2O \xrightarrow[\substack{20\ °C}]{\substack{benzene, \\ -\ HC(SiMe_3)_3,\ -\ C_2H_4}} 0.5\ [C(SiMe_3)_3Yb(\mu\text{-}OEt)(OEt_2)]_2 \quad (66)$$

$$Cp_2Yb(CH_3)(thf)\ /\ LiCl(thf)_x \xrightarrow[\substack{reflux\ ,\ 72\ h}]{\substack{toluene,\ -\ THF}} [Cp_2Yb(\mu\text{-}OCH=CH_2)]_2 \quad (67)$$

(68)

$$YCl_3 + 2\ NaCp + Li(CH_2)_3NMe_2 \xrightarrow[\substack{-\ 2\ NaCl,\ -\ LiCl}]{\substack{THF\ /\ CO_2\ (dry\ ice)}} \quad (69)$$

$$2 \ (C_5H_4tBu)_3Ln \xrightarrow[\text{-35 °C}]{\substack{\text{crystallization} \\ \text{hexane / H}_2\text{O (traces)}}} [(C_5H_4tBu)_2Ln(\mu\text{-OH})]_2 \quad + \quad 2 \ HCptBu \qquad (70)$$

$$3 \ Ce(OtBu)_4(thf)_2 \xrightarrow[\text{rt, 2-3d}]{\text{toluene, -THF}} Ce_3(OtBu)_{10}O \qquad (71)$$

6
Perspectives

Examples of the exceptional and intriguing potential of rare earth reagents in organic synthesis will be treated in comprehensive form in the following chapters of this volume. The text of this chapter on "Principles in Organolanthanide Chemistry" has been directed towards a basic understanding of the chemistry of the most reactive members of this family. Improved and alternative synthetic procedures ensure the availability of both inorganic and organometallic reagents in pure and well-defined form. Each of the important areas of reactivity of organolanthanide compounds which have been addressed to in this survey should prove fertile for further development. Examination of such highly reactive species will provide important details to explain the reaction pathways of the inorganic reagents in organic synthesis by means of spectroscopy and structure determination. So far, the vast majority of active components and reaction intermediates is under-determined due to the application of in situ reaction sequences. The operating system is often a "black-box" and process optimization is achieved by empirical methods. This dearth of data of the active components should further stimulate the interaction between organic synthesis and organometallic chemistry. On the other hand, chiral organometallic and pseudo-organometallic reagents challenge the field of enantioselective catalysis. For this relatively young branch of lanthanide chemistry, ligand design has become indispensable. Since rare earth ligand interactions are ruled by simple principles such as ionic bonding and the HSAB theory, combinatorial chemistry could prove a valuable tool for ligand fine-tuning. In addition to the evaluation of novel ancillary ligand sets, detailed studies on supramolecular rare earth chemistry are to be expected, tackling host-guest interactions [322], the topic of immobilization [235], and dendrimer chemistry [323]. Clearly, organolanthanide chemistry has much to offer to the field of organic synthesis.

7
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Lanthanide Triflate-Catalyzed Carbon-Carbon Bond-Forming Reactions in Organic Synthesis

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Versatile carbon-carbon bond-forming reactions using lanthanide triflates $(Ln(OTf)_3)$ as catalysts are discussed. Lanthanide triflates are new types of Lewis acids different from typical Lewis acids such as $AlCl_3$, BF_3, $SnCl_4$, etc. While most Lewis acids are decomposed or deactivated in the presence of water, lanthanide triflates are stable and works as Lewis acids in water solutions. Many nitrogen-containing compounds such as imines and hydrazones are also successfully activated by using a small amount of $Ln(OTf)_3$. Lanthanide triflates are also excellent Lewis acid catalysts in organic solvents. A catalytic amount of $Ln(OTf)_3$ is enough to complete reactions in most cases. In addition, $Ln(OTf)_3$ can be recovered after reactions are completed and can be reused. Several chiral lanthanide catalysts for asymmetric Diels-Alder, aza Diels-Alder, and 1,3-dipolar cycloaddition reactions are also described.

Keywords: Lanthanide triflate, Lewis acid, Carbon-carbon bond formation, Asymmetric synthesis, Catalysis, Organic synthesis

1
Introduction

Lewis acid-catalyzed carbon-carbon bond forming reactions have been of great interest in organic synthesis because of their unique reactivities, selectivities, and for the mild conditions used [1]. While various kinds of Lewis acid-promoted reactions have been developed and many have been applied in industry, these reactions must be carried out under strict anhydrous conditions. The presence of even a small amount of water stops the reaction because most Lewis acids immediately react with water rather than the substrates and decompose or deactivate, and this has restricted the use of Lewis acids in organic synthesis.

On the other hand, lanthanide compounds were expected to act as strong Lewis acids because of their hard character and to have strong affinity toward carbonyl oxygens [2]. Among these compounds, lanthanide triflates ($Ln(OTf)_3$) were expected to be one of the strongest Lewis acids because of the electron-withdrawing trifluoromethanesulfonyl group. Their hydrolysis was postulated to be slow, based on their hydration energies and hydrolysis constants [3]. In fact, while most metal triflates are prepared under strict anhydrous conditions, Lanthanide triflates are reported to be prepared in aqueous solution [4, 5]. The large radius and the specific coordination number of lanthanide(III) are also unique, and many investigations using $Ln(OTf)_3$ as Lewis acids have been performed.

In this paper, use of $Ln(OTf)_3$ as Lewis acid catalysts in carbon-carbon bond-forming reactions in both aqueous and organic solvents is overviewed.

2
Aldol Reactions

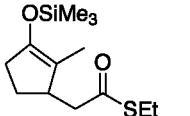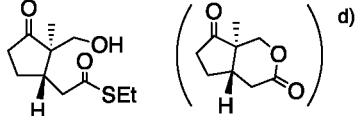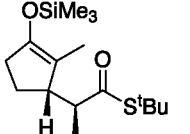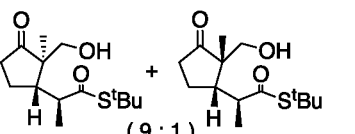## 2.1
Aldol Reactions in Aqueous Media
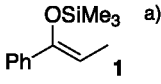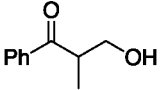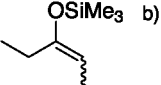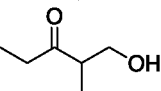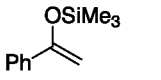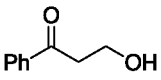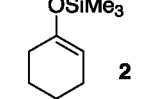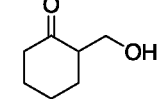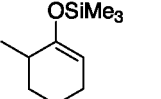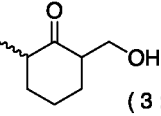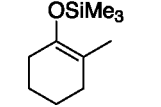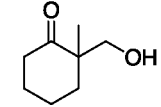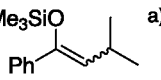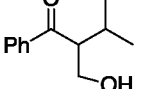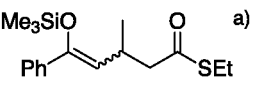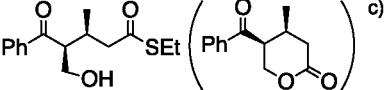
The titanium tetrachloride-mediated aldol reaction of silyl enol ethers with aldehydes was first reported in 1973 [6]. The reaction is notably distinguished from the conventional aldol reactions carried out under basic conditions; it proceeds in a highly regioselective manner to afford cross aldols in high yields [7]. Since this pioneering effort, several efficient activators such as trityl salts [8], Cray montmorillonite [9], fluoride anions [10], etc. [11] have been developed to realize high yields and selectivities, and now the reaction is considered to be one of the most important carbon-carbon bond forming reactions in organic synthesis. These reactions are usually carried out under strictly anhydrous conditions. The presence of even a small amount of water causes lower yields, probably due to the rapid decomposition or deactivation of the promoters and the hydrolysis of the silyl enol ethers. Furthermore, the promoters cannot be recovered and reused because they decompose under usual quenching conditions.

On the other hand, the water-promoted aldol reaction of silyl enol ethers with aldehydes was reported in 1986 [12]. While the report that the aldol reactions proceeded without catalyst in water was unique, the yields and the substrate scope were not satisfactory. In 1991 the first example of Lewis acid catalysis in aqueous media was reported; that is the hydroxymethylation reaction of silyl enol ethers with commercial formaldehyde solution using $Ln(OTf)_3$. Formaldehyde is a versatile reagent as one of the most highly reactive C1 electrophiles in organic synthesis [13]. Dry gaseous formaldehyde required for many reactions has some disadvantages because it must be generated before use from solid polymer paraformaldehyde by way of thermal depolymerization and it itself-polymerizes easily [14]. On the other hand, commercial formaldehyde solution, which is an aqueous solution containing 37% formaldehyde and 8–10% methanol, is cheap, easy to handle, and stable even at room temperature. However, the use of this reagent is strongly restricted due to the existence of a large amount of water. For example, the titanium tetrachloride ($TiCl_4$)-promoted hydroxymethylation reaction of silyl enol ethers was carried out by using trioxane as a HCHO source under strict anhydrous conditions [6b, 15]. Formaldehyde water solution could not be used because $TiCl_4$ and the silyl enol ether reacted with water rather than HCHO in that water solution.
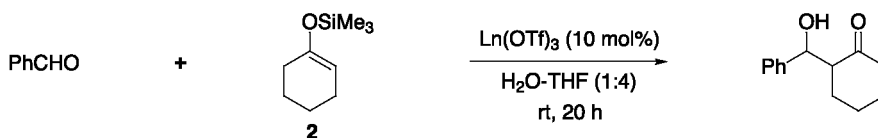
The effects of $Ln(OTf)_3$ in the reaction of 1-phenyl-1-trimethylsiloxypropene (1) with commercial formaldehyde solution were examined [16]. In most cases the reactions proceeded smoothly to give the corresponding adducts in high yields. The reactions were most effectively carried out in commercial formaldehyde solution-THF media under the influence of a catalytic amount of $Yb(OTf)_3$.

Several examples of the hydroxymethylation reaction of silyl enol ethers with commercial formaldehyde solution are shown in Table 1, and the following char-

Table 1. Reaction of silyl enol ethers with commercial formaldehyde solution catalyzed by Yb(OTf)$_3$

Entry	Silyl enol ether	Product	Yield/%
1			94
2			85
3			77
4			82
5		(3:2)	86
6			92
7			92
8			88
9			83
10		(9:1)	90

[a] $Z/E=>98/2$.

[b] $Z/E=1/4$.

[c] The mixture of the hydroxy thioester and the lactone (2:1) was obtained. The other diastereomers were not observed.

[d] The mixture of the hydroxy thioester and lactone (3:1) was obtained. Less than 3% yield of the other diastereomers was observed.

$$\text{PhCHO} \quad + \quad \underset{\textbf{2}}{\text{(1-trimethylsiloxycyclohexene, OSiMe}_3\text{)}} \quad \xrightarrow[\substack{H_2O\text{-THF (1:4)} \\ \text{rt, 20 h}}]{Ln(OTf)_3 \ (10 \ mol\%)} \quad \text{Ph} \overset{OH}{\underset{}{\diagdown}} \overset{O}{\diagup}$$

Table 2. Effect of Lanthanide Triflates

$Ln(OTf)_3$	Yield/%	$Ln(OTf)_3$	Yield/%
$La(OTf)_3$	8	$Dy(OTf)_3$	73
$Pr(OTf)_3$	28	$Ho(OTf)_3$	47
$Nd(OTf)_3$	83	$Er(OTf)_3$	52
$Sm(OTf)_3$	46	$Tm(OTf)_3$	20
$Eu(OTf)_3$	34	$Yb(OTf)_3$	91
$Gd(OTf)_3$	89	$Lu(OTf)_3$	88

acteristic features of this reaction are noted. (1) In every case, the reactions proceeded smoothly under extremely mild conditions (almost neutral) to give the corresponding hydroxymethylated adducts in high yields. Sterically hindered silyl enol ethers also worked well and the diastereoselectivities were high. (2) Di- and poly-hydroxymethylated products were not observed [17]. (3) The absence of equilibrium (double bond migration) in silyl enol ethers allowed for a regiospecific hydroxymethylation reaction. (4) Only a catalytic amount of $Yb(OTf)_3$ was required to complete the reaction. The amount of the catalyst was examined by taking the reaction of 1 with commercial formaldehyde solution as a model, and the reaction was found to be catalyzed by even 1 mol% of $Yb(OTf)_3$: 1 mol% (90% yield); 5 mol% (90% yield); 10 mol% (94% yield); 20 mol% (94% yield); 100 mol% (94% yield).

The use of $Ln(OTf)_3$ in the activation of aldehydes other than formaldehyde was also investigated [18]. The model reaction of 1-trimethylsiloxycyclohexene (2) with benzaldehyde under the influence of a catalytic amount of $Yb(OTf)_3$ (10 mol%) was examined. The reaction proceeded smoothly in H_2O-THF (1:4), but the yields were low when water or THF was used alone. Among several $Ln(OTf)_3$ screened, neodymium triflate ($Nd(OTf)_3$), gadolinium triflate ($Gd(OTf)_3$), $Yb(OTf)_3$, and lutetium triflate ($Lu(OTf)_3$) were quite effective, while the yield of the desired aldol adduct was lower in the presence of lanthanum triflate ($La(OTf)_3$), praseodymium triflate ($Pr(OTf)_3$) or thulium triflate ($Tm(OTf)_3$) (Table 2).

Lanthanide triflates were found to be effective for the activation of formaldehyde water solution. The effect of ytterbium salts was also investigated (Table 3) [19]. While the Yb salts with less nucleophilic counter anions such as OTf^- or ClO_4^- effectively catalyzed the reaction, only low yields of the product were obtained when the Yb salts with more nucleophilic counter anions such as Cl^-, OAc^-, NO_3^-, and SO_4^{2-} were employed. The Yb salts with less nucleophilic coun-

PhCHO   +   [structure: OSiMe₃ cyclohexene, **2**]   →[Yb salt (10 mol%), H₂O-THF (1:4), rt, 19 h]→   [product: Ph—CH(OH)—cyclohexanone]
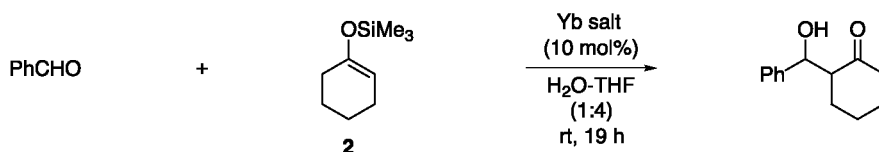
Table 3. Effect of Yb salts

Yb salt	Yield/%
Yb(OTf)$_3$	91 [a]
Yb(ClO)$_4$	88 [b]
YbCl$_3$	3
Yb(OAc)$_3$•8H$_2$O	14
Yb(NO$_3$)$_3$•5H$_2$O	7
Yb$_2$(SO$_4$)$_3$•5H$_2$O	trace

[a] *syn/anti* = 73/27
[b] 76/24
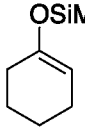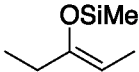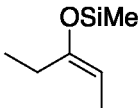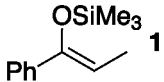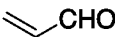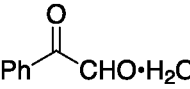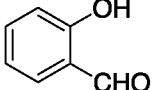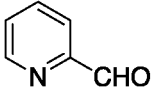
ter anions are more cationic and the high Lewis acidity promotes the desired reaction.

Several examples of the present aldol reaction of silyl enol ethers with aldehydes are listed in Table 4. In every case, the aldol adducts were obtained in high yields in the presence of a catalytic amount of Yb(OTf)$_3$, Gd(OTf)$_3$, or Lu(OTf)$_3$ in aqueous media. Diastereoselectivities were generally good to moderate. One feature in the present reaction is that water soluble aldehydes, for instance, acetaldehyde, acrolein, and chloroacetaldehyde, can be reacted with silyl enol ethers to afford the corresponding cross aldol adducts in high yields (entries 5–7). Some of these aldehydes are commercially supplied as water solutions and are appropriate for direct use. Phenylglyoxal monohydrate also worked well (entry 8). It is known that water often interferes with the aldol reactions of metal enolates with aldehydes and that in the cases where such water soluble aldehydes are employed, some troublesome purifications including dehydration are necessary. Moreover, salicylaldehyde (entry 9) and 2-pyridinecarboxaldehyde (entry 10) could be successfully employed. The former has a free hydroxy group which is incompatible with metal enolates or Lewis acids, and the latter is generally difficult to use under the influence of Lewis acids because of the coordination of the nitrogen atom to the Lewis acids resulting in the deactivation of the acids.

The aldol reactions of silyl enol ethers with aldehydes were also found to proceed smoothly in water-ethanol-toluene [20]. Some reactions proceeded much faster in this solvent system than in THF-water. Furthermore, the new solvent system realized continuous use of the catalyst by a very simple procedure.

Several water-organic solvent systems were examined in the model reaction of 1-phenyl-1-trimethylsiloxypropene (1) with 2-pyridinecarboxaldehyde un-

$$R^1CHO \quad + \quad \underset{R^2}{\overset{OSiMe_3}{\diagdown}}R^3 \quad \xrightarrow[\text{H}_2\text{O-THF, rt}]{\substack{\text{Yb(OTf)}_3 \\ (10 \text{ mol\%})}} \quad R^1\underset{R^3}{\overset{OH \quad O}{\diagdown}}R^2$$

Table 4. Lanthanide triflate-catalyzed aldol reactions in aqueous media

Entry	Aldehyde	Silyl Enol Ether	Yield/%
1	PhCHO	(cyclohexenyl OSiMe₃) **2**	91 [a)]
2	PhCHO	(OSiMe₃ enol ether)	89 [b)]
3	PhCHO	(OSiMe₃ enol ether)	93 [c)]
4	PhCHO	Ph (OSiMe₃) **1**	81 [d)]
5	CH₃CHO	**1**	93 [e, f)]
6	(CH₂=CH-CH=CH-CHO)	**1**	82 [e, g)]
7	Cl—CHO	**1**	95 [h)]
8	Ph-C(O)-CHO·H₂O	**1**	67 [i)]
9	(2-hydroxybenzaldehyde)	**1**	81 [j, k)]
10	(pyridine-2-carbaldehyde)	**1**	87 [j, l)]

[a] *syn/anti=73/27.*
[b] *syn/anti=63/37.*
[c] *syn/anti=71/29.*
[d] *syn/anti=53/47.*
[e] Gd(OTf)₃ was used instead of Yb(OTf)₃.
[f] *syn/anti=46/54.*
[g] *syn/anti=60/40.*
[h] *syn/anti=45/55.*
[i] *syn/anti=27/73.*
[j] Lu(OTf)₃ was used instead of Yb(OTf)₃.
[k] *syn/anti=55/45.*
[l] *syn/anti=42/58.*
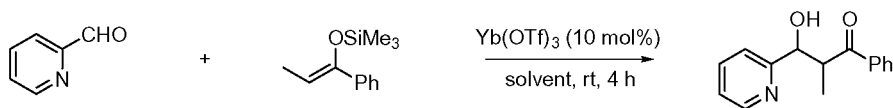
Table 5. Effect of solvents

Solvent		Yield / %	syn/anti
H$_2$O / Toluene (1 : 4)		0	——
H$_2$O / EtOH / Toluene	(1 : 3 : 4)	30	37 / 63
	(1 : 5 : 4)	41	39 / 61
	(1 : 7 : 4)	70	41 / 59
	(1 : 10 : 4)	96	40 / 60
H$_2$O / THF (1 : 4)		12	43 / 57

der the influence of 10 mol% Yb(OTf)$_3$ (Table 5). While the reaction proceeded sluggishly in a water-toluene system, the adduct was obtained in a good yield when ethanol was added to this system. The yield increased in accordance with the amount of ethanol, and it was noted that the reaction proceeded much faster in the water-ethanol-toluene system than in the original water-THF system.

Although the water-ethanol-toluene (1:7:4) system was one phase, it easily became two phases by adding toluene after the reaction was completed. The product was isolated from the organic layer by a usual work up. On the other hand, the catalyst remained in the aqueous layer, which was used directly in the next reaction without removing water. It is noteworthy that the yields of the second, third, and fourth runs were comparable to that of the first run (Eq. 1).

$$\text{(1)}$$

1st run: 86% (syn/anti = 38/62)
2nd run: 82% (syn/anti = 38/62)
3rd run: 90% (syn/anti = 38/62)
4th run: 82% (syn/anti = 39/61)
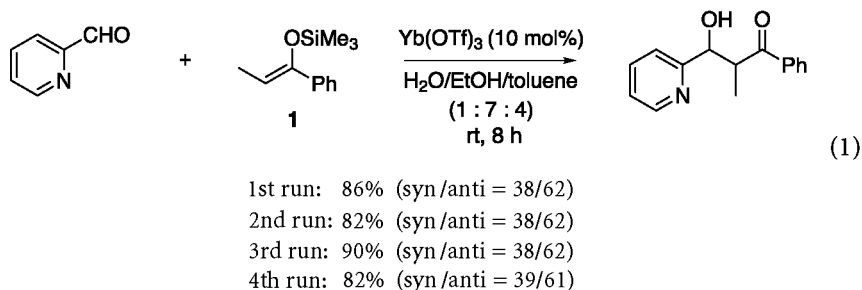
Several examples of the present aldol reactions of silyl enol ethers with aldehydes in water-ethanol-toluene are listed in Table 6. 3-Pyridinecarboxaldehyde as well as 2-pyridinecarboxaldehyde, salicylaldehyde, and formaldehyde water
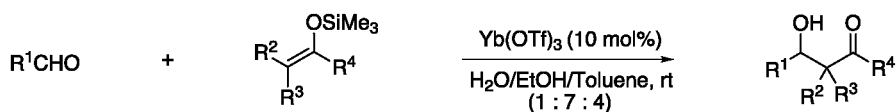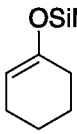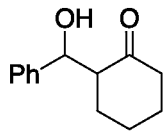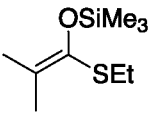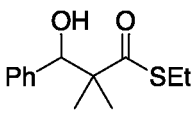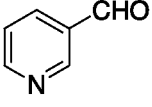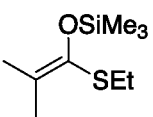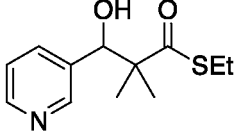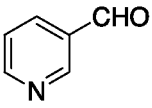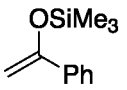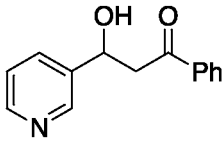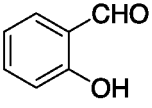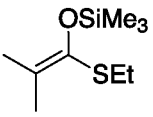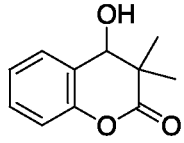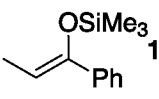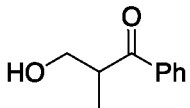
Table 6. b(OTf)$_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes in water-ethanol-toluene

Aldehyde	Silyl Enol Ether	Product	Yield / %
PhCHO	**2**		89 [a)]
PhCHO			95
			87
			82
			96
HCHO aq.	**1**		90

[a] *syn/anti=74/26.*

solution worked well. As for silyl enol ethers, not only ketone enol ethers but also silyl enolates derived from thioesters were used. In every case, the adducts were obtained in high yields in the presence of 10 mol% Yb(OTf)$_3$.

```
                          ┌──────────────────┐
                          │ reaction mixture │
                          └──────────────────┘
                                    │
                           water (quench)
                                    │
                         ┌──────────┴──────────┐
        (extraction)     │                     │
                         ▼                     ▼
                ┌───────────────┐      ┌───────────────┐
                │ organic layer │      │ aqueous layer │
                └───────────────┘      └───────────────┘
                        │                      │
               (purification)        (removal of water)
                        │                      │
                        ▼                      ▼
                ┌───────────┐          ┌───────────┐
                │  product  │          │  Ln(OTf)₃ │
                └───────────┘          └───────────┘
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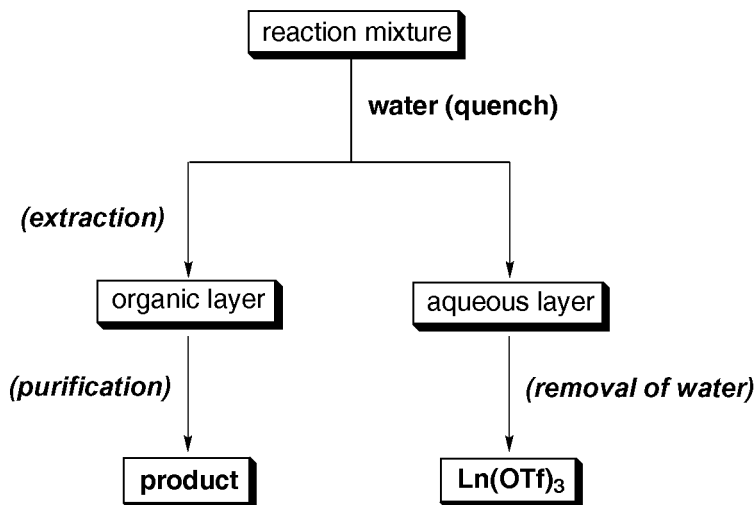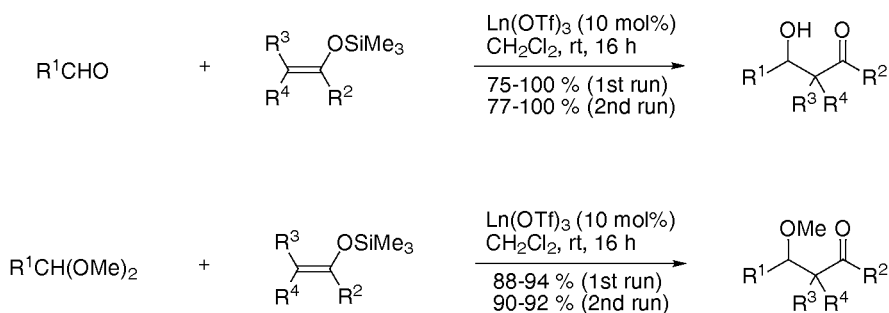
Scheme 1

2.2
Recovery and Reuse of the Catalyst

While continuous use of $Ln(OTf)_3$ is possible, it is also easy to recover $Ln(OTf)_3$ themselves. Lanthanide triflates are more soluble in water than in organic solvents such as dichloromethane. Almost 100% of $Ln(OTf)_3$ was quite easily recovered from the aqueous layer after the reaction was completed and it could be reused. For example, first use (20 mol% of $Yb(OTf)_3$) in the reaction of 1 with formaldehyde water solution (94% yield); second use (91% yield); third use (93% yield). The reactions are usually quenched with water and the products are extracted with an organic solvent (for example, dichloromethane). Lanthanide triflate is in aqueous layer and only removal of water gives the catalyst which can be used in the next reaction (Scheme 1). It is noteworthy that lanthanide triflates are expected to solve some severe environmental problems induced by Lewis acid-promoted reactions in industrial chemistry [21].

2.3
Aldol Reactions in Organic Solvents

Lanthanide triflates were found to be excellent Lewis acids not only in aqueous media but also in organic solvents. The reaction of ketene silyl acetal 3 with benzaldehyde proceeded smoothly in the presence of 10 mol% of $Yb(OTf)_3$ in dichloromethane at –78 °C, to afford the corresponding aldol-type adduct in a 94% yield. The same reaction at room temperature also went quite cleanly without side reactions and the desired adduct was obtained in a 95% yield. No adduct
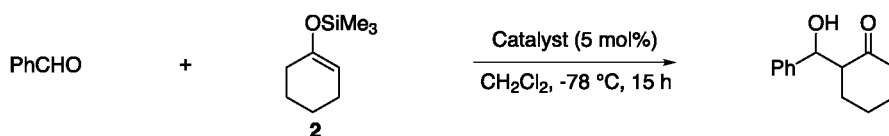
R^1CHO +   [structure: R^3, OSiMe$_3$, R^4, R^2] $\xrightarrow[\substack{75\text{-}100\ \%\ (1st\ run)\\77\text{-}100\ \%\ (2nd\ run)}]{\substack{Ln(OTf)_3\ (10\ mol\%)\\CH_2Cl_2,\ rt,\ 16\ h}}$ [structure: R^1, OH, O, R^2, R^3 R^4]

$R^1CH(OMe)_2$ +   [structure: R^3, OSiMe$_3$, R^4, R^2] $\xrightarrow[\substack{88\text{-}94\ \%\ (1st\ run)\\90\text{-}92\ \%\ (2nd\ run)}]{\substack{Ln(OTf)_3\ (10\ mol\%)\\CH_2Cl_2,\ rt,\ 16\ h}}$ [structure: R^1, OMe, O, R^2, R^3 R^4]

Scheme 2

PhCHO   +   [structure: OSiMe$_3$ cyclohexene] **2** $\xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{-78 °C, 15 h}]{\text{Catalyst (5 mol\%)}}$ [structure: Ph, OH, O cyclohexanone]

Table 7. Effect of catalysts

Entry	Catalyst	Yield/%
1	Sc(OTf)$_3$	81
2	Y(OTf)$_3$	trace
3	Yb(OTf)$_3$	trace

was obtained in THF-water or toluene-ethanol-water, because hydrolysis of the ketene silyl acetal preceded the desired aldol reaction in such solvents. In other organic solvents such as toluene, THF, acetonitrile, and DMF, Yb(OTf)$_3$ worked well, and it was found that other Ln(OTf)$_3$ also catalyzed the above aldol reaction effectively (85–95% yields).

Silyl enolates derived from not only esters but also thioesters and ketones reacted with aldehydes to give the corresponding adducts in high yields (Scheme 2) [22]. Furthermore, acetals reacted smoothly with silyl enolates to afford the corresponding aldol-type adducts in high yields. It should be noted that the catalysts could be easily recovered from the aqueous layer after the reactions were quenched with water and could be reused, and that the yields of the second run were almost comparable to those of the first run in every case.

Scandium triflate (Sc(OTf)$_3$) was found to be an effective catalyst in the aldol reactions [23]. The activities of various triflate catalysts were evaluated in the aldol reaction of 1-trimethylsiloxycyclohexene (2) with benzaldehyde in dichloromethane (Table 7). While the reaction scarcely proceeded at –78 °C in the presence of Yb(OTf)$_3$ or Y(OTf)$_3$ [24], the aldol adduct was obtained in an 81%
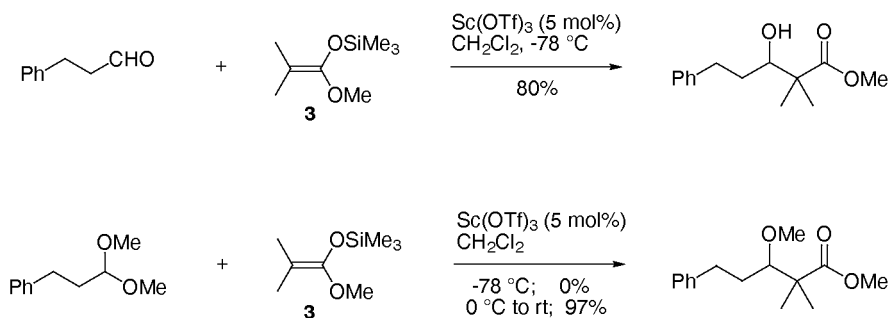
Scheme 3

yield in the presence of Sc(OTf)$_3$. Obviously Sc(OTf)$_3$ is more active than Y(OTf)$_3$ or Yb(OTf)$_3$ in this case.

Several examples of the Sc(OTf)$_3$-catalyzed aldol reactions of silyl enolates with aldehydes were examined, and it was found that silyl enolates derived from ketones, thioesters, and esters reacted smoothly with aldehydes in the presence of 5 mol% of Sc(OTf)$_3$ to afford the aldol adducts in high yields. Sc(OTf)$_3$ was also found to be an effective catalyst in the aldol-type reaction of silyl enolates with acetals. The reactions proceeded smoothly at –78 °C or room temperature to give the corresponding aldol-type adducts in high yields without side reaction products. It should be noted that aldehydes were more reactive than acetals [25]. For example, while 3-phenylpropionaldehyde reacted with the ketene silyl acetal of methyl 2-methylpropionate (3) at –78 °C to give the aldol adduct in an 80% yield, no reaction occurred at –78 °C in the reaction of the same ketene silyl acetal with 3-phenylpropionaldehyde dimethylacetal. The acetal reacted with the ketene silyl acetal at 0 °C to room temperature to give the aldol-type adduct in a 97% yield (Scheme 3).

Sc(OTf)$_3$ can behave as a Lewis acid catalyst even in aqueous media. Sc(OTf)$_3$ was stable in water and was effective in the aldol reactions of silyl enolates with aldehydes in aqueous media. The reactions of usual aromatic and aliphatic aldehydes such as benzaldehyde and 3-phenylpropionaldehyde with silyl enolates were carried out in both aqueous and organic solvents, and water-soluble formaldehyde and chloroacetaldehyde were directly treated as water solutions with silyl enolates to afford the aldol adducts in good yields. Moreover, the catalyst could be recovered almost quantitatively from the aqueous layer after the reaction was completed. The recovered catalyst was also effective in the second reaction, and the yield of the second run was comparable to that of the first run (Eq. 2).
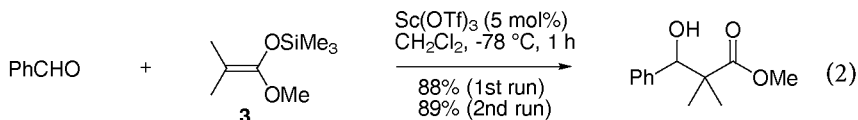
2.4
Aldol Reactions in Micellar Systems

$Sc(OTf)_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes were successfully carried out in micellar systems. While the reactions proceeded sluggishly in pure water, remarkable enhancement of the reactivity was observed in the presence of a small amount of a surfactant. In these systems, versatile carbon-carbon bond-forming reactions proceeded in water without using any organic solvents.

Lewis acid catalysis in micellar systems was first found in the model reaction of 1 with benzaldehyde (Table 8) [26]. While the reaction proceeded sluggishly in the presence of 0.2 equiv. $Yb(OTf)_3$ in water, remarkable enhancement of the reactivity was observed when the reaction was carried out in the presence of 0.2 equiv. $Yb(OTf)_3$ in an aqueous solution of sodium dodecylsulfate (SDS, 0.2 equiv., 35 mmol/l), and the corresponding aldol adduct was obtained in a 50% yield. In the absence of the Lewis acid and the surfactant (water-promoted conditions), only 20% yield of the aldol adduct was isolated after 48 h, while a 33% yield of the aldol adduct was obtained after 48 h in the absence of the Lewis acid in an aqueous solution of SDS. The amounts of the surfactant also influ-
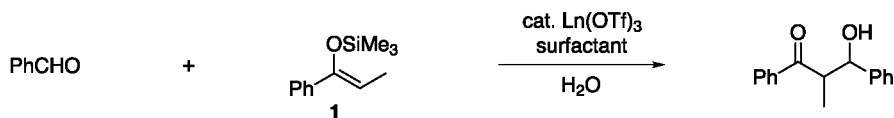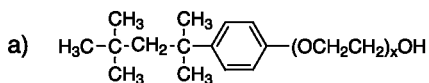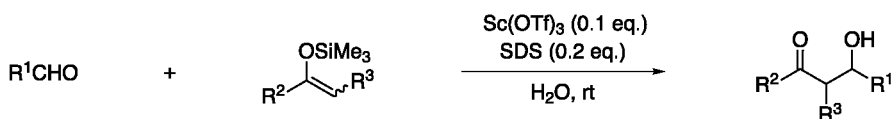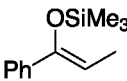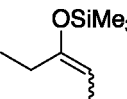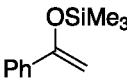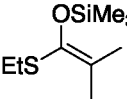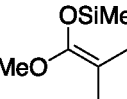
Table 8. Effect of $Ln(OTf)_3$ and surfactants

$Ln(OTf)_3$/eq.	Surfactant/equiv.	Time/h	Yield/%
$Yb(OTf)_3$/0.2	——	48	17
$Yb(OTf)_3$/0.2	SDS/0.04	48	12
$Yb(OTf)_3$/0.2	SDS/0.1	48	19
$Yb(OTf)_3$/0.2	SDS/0.2	48	50
$Yb(OTf)_3$/0.2	SDS/1.0	48	22
$Sc(OTf)_3$/0.2	SDS/0.2	17	73
$Sc(OTf)_3$/0.1	SDS/0.2	4	88
$Sc(OTf)_3$/0.1	TritonX-100 [a)]/0.2	60	89
$Sc(OTf)_3$/0.1	CTAB/0.2	4	trace

a) $H_3C-C(CH_3)_2-CH_2-C(CH_3)_2-C_6H_4-(OCH_2CH_2)_xOH$

$$R^1CHO \quad + \quad \underset{R^2}{\overset{OSiMe_3}{\diagup}}\diagdown R^3 \quad \xrightarrow[\text{H}_2\text{O, rt}]{\substack{Sc(OTf)_3 \ (0.1 \ eq.) \\ SDS \ (0.2 \ eq.)}} \quad \underset{R^3}{\overset{O \quad OH}{R^2\diagdown\diagup R^1}}$$

Table 9. $Sc(OTf)_3$-catalyzed aldol reactions in micellar systems

Aldehyde	Silyl Enol Ether	Yield/%
PhCHO	$\underset{Ph}{\overset{OSiMe_3}{\diagdown}}$ **1**	88 [a]
Ph⌒CHO	**1**	86 [b]
Ph⌒CHO	**1**	88 [c]
HCHO	**1**	82 [d]
PhCHO	$\overset{OSiMe_3}{\diagdown}$	88 [e]
PhCHO	$\underset{Ph}{\overset{OSiMe_3}{\diagdown}}$	75 [f,g]
PhCHO	$\underset{EtS}{\overset{OSiMe_3}{\diagdown}}$	94
PhCHO	$\underset{MeO}{\overset{OSiMe_3}{\diagdown}}$ **3**	84 [g]

[a] *syn/anti*=50/50.
[b] *syn/anti*=45/55.
[c] *syn/anti*=41/59.
[d] Commercially available HCHO aq. (3 ml), **1** (0.5 mmol), $Sc(OTf)_3$ (0.1 mmol), and SDS (0.1 mmol) were combined.
[e] *syn/anti*=57/43.
[f] $Sc(OTf)_3$ (0.2 equiv.) was used.
[g] Additional silyl enolate (1.5 equiv.) was charged after 6 h.

enced the reactivity and the yield was improved when $Sc(OTf)_3$ was used as a Lewis acid catalyst. Judging from the critical micelle concentration, micelles would be formed in these reactions, and it is noteworthy that the Lewis acid-catalyzed reactions proceeded smoothly in micellar systems [27]. It was also found that the surfactants influenced the yield, and that TritonX-100 was effective in the aldol reaction (but required long reaction time), while only a trace amount of the adduct was detected when using cetyltrimethylammonium bromide (CTAB) as a surfactant [28].

Several examples of the Sc(OTf)$_3$-catalyzed aldol reactions in micellar systems are shown in Table 9. Not only aromatic, but also aliphatic and a,b-unsaturated aldehydes reacted with silyl enol ethers to afford the corresponding aldol adducts in high yields. Formaldehyde water solution also worked well. Ketene silyl acetal **3**, which is known to hydrolyze very easily even in the presence of a small amount of water, reacted with an aldehyde in the present micellar system to afford the corresponding aldol adduct in a high yield.

It should be noted that the reactions were successfully carried out in water without using any organic solvents. Use of the reusable scandium catalyst and water as a solvent would result in clean and environmentally friendly systems.

3
Diels-Alder Reactions

Although many Diels-Alder reactions have been carried out at higher reaction temperatures without catalysts, heat sensitive compounds in complex and multistep syntheses cannot be employed. While Lewis acid catalysts allow the reactions to proceed at room temperature with satisfactory yields, they are often accompanied by diene polymerization and excess amounts of the catalyst are often needed to catalyze carbonyl-containing dienophiles [29].

Lanthanide triflates were also found to be efficient catalysts in the Diels-Alder reactions of carbonyl-containing dienophiles with cyclopentadiene [30]. A catalytic amount of Yb(OTf)$_3$ was enough to promote the reactions to give the corresponding adducts in high yields, and the catalyst could be easily recovered and reused.

In the Diels-Alder reactions, Sc(OTf)$_3$ was clearly the most effective among Ln(OTf)$_3$ as a catalyst [31]. While in the presence of 10 mol% of Y(OTf)$_3$ or Yb(OTf)$_3$, only a trace amount of the adduct was obtained in the Diels-Alder reaction of MVK with isoprene, and the reaction proceeded quite smoothly to give the adduct in a 91% yield in the presence of 10 mol% of Sc(OTf)$_3$.
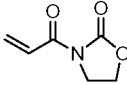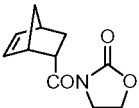
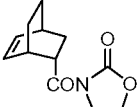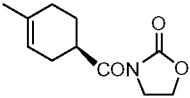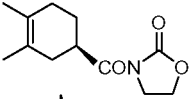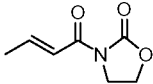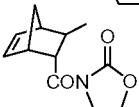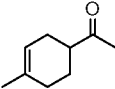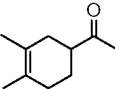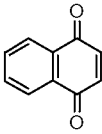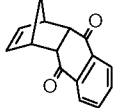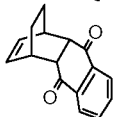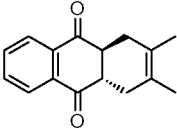Several examples of the Sc(OTf)$_3$-catalyzed Diels-Alder reactions are shown in Table 10. In every case, the Diels-Alder adducts were obtained in high yields with *endo* selectivities.

The present Diels-Alder reactions proceeded even in aqueous media (Eq. 3) [32]. Thus, naphthoquinone reacted with cyclopentadiene in THF-H$_2$O (9:1) at room temperature to give the corresponding adduct in a 93% yield (*endo/exo*= 100/0).

$$\text{Sc(OTf)}_3 \ (10 \text{ mol\%})$$
$$\text{THF} : \text{H}_2\text{O} \ (\ 9 : 1\ )$$
93% yield, *endo/exo* = 100/ 0

(3)
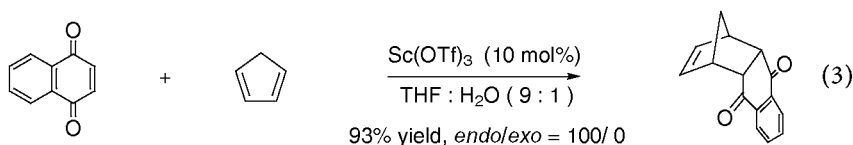
Recovery and reuse of the catalyst were also possible in this reaction. After the reaction was completed, the aqueous layer was concentrated to give the catalyst. The recovered catalyst was effective in subsequent Diels-Alder reactions, and it

Table 10. Sc(OTf)$_3$-catalyzed Diels-Alder reactions

Dienophile	Diene	Product	Yield /%	endo/exo
			95	87 / 13
			89	100 / 0
			90	—
			86	—
			97	84 / 16
			96	89 / 11
			83	>95 / 5
			91	—
			73	—
			83	100 / 0
			89	94 / 3
			92	—

should be noted that the yields of the second and even the third runs were comparable to that of the first run.

4
Allylation Reactions

Synthesis of homoallylic alcohols by the reaction of allyl organometallics with carbonyl compounds is one of the most important processes in organic synthesis [33]. The allylation reactions of carbonyl compounds were found to proceed smoothly under the influence of 5 mol% of $Sc(OTf)_3$ [34] by using tetraallyltin [35] as an allylating reagent [36]. Several examples are shown in Table 11. The reactions proceeded smoothly in the presence of only a catalytic amount of $Sc(OTf)_3$ under extremely mild conditions [8], and the adducts, homoallylic alcohols, were obtained in high yields. Ketones could also be used in the reaction (entries 4, 5). In most cases, the reactions were successfully carried out in aqueous media. It is noteworthy that unprotected sugars reacted directly to give the adducts in high yields (entries 7–9). The allylated adducts are intermediates for the synthesis of higher sugars [37]. Moreover, an aldehyde containing water of crystallization such as phenylglyoxal monohydrate reacted with tetraallyltin to give the di-allylated adduct in high yield (entry 10). Under the present reaction conditions, salicylaldehyde and 2-pyridinecarboxaldehyde reacted with tetraallyltin to afford the homoallylic alcohols in good yields (entries 11, 12). Under general Lewis acid conditions, these compounds react with the Lewis acids rather than the nucleophile. Furthermore, several kinds of solvents could be used. The reactions also proceeded under non-aqueous conditions. Water-sensitive substrates under Lewis acid conditions could be reacted in an appropriate organic solvent (entries 13, 14).

$Yb(OTf)_3$ is also effective in the present allylation reactions. For example, 3-phenylpropionaldehyde reacted with tetraallyltin in the presence of 5 mol% of $Yb(OTf)_3$ to afford the adduct in a 90% yield.

The water-ethanol-toluene system could be successfully applied to the present allylation reactions. An example of the allylation reaction of tetraallyltin with aldehyde is shown in Eq. (4), and in this case continuous use of the catalyst was also realized.

$$Ph\diagdown\diagdown CHO \quad + \quad (\diagdown\diagdown)_4Sn \quad \xrightarrow[\substack{H_2O/EtOH/toluene \\ (1:7:4) \\ rt, 8\ h}]{Yb(OTf)_3\ (10\ mol\%)} \quad Ph\diagdown\diagdown\overset{OH}{\diagdown}\diagdown\diagdown \qquad (4)$$
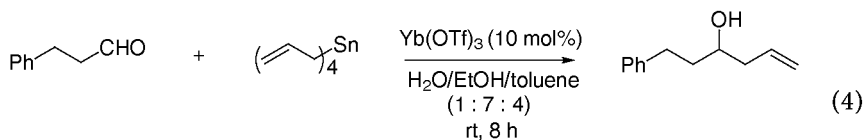
1st run: 90%; 2nd run: 95%; 3rd run: 96%; 4th run: 89%

Furthermore, the $Sc(OTf)_3$-catalyzed allylation reactions of aldehydes with tetraallyltin proceeded smoothly in micellar systems to afford the correspond-

Table 11. Sc(OTf)$_3$-catalyzed allylation reactions of carbonyl compounds with tetraallyltin[a]
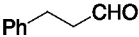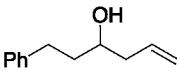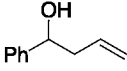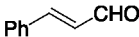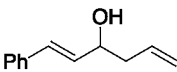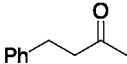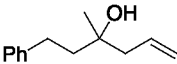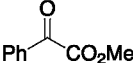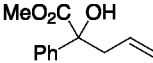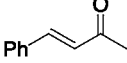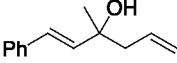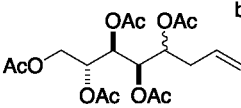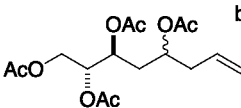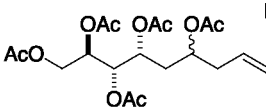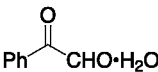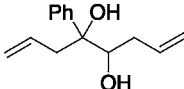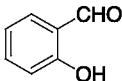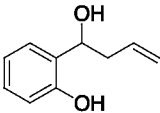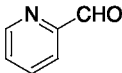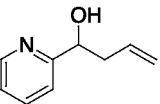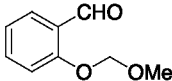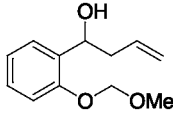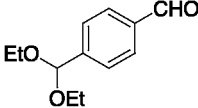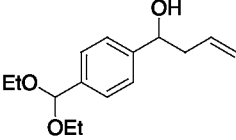
Entry	Carbonyl Compound	Product	Solvent	Yield/%
1	Ph–CH$_2$CH$_2$–CHO	Ph–CH$_2$CH$_2$–CH(OH)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	92
			H$_2$O : EtOH (1:9)	96
			H$_2$O : CH$_3$CN (1:9)	96
			EtOH	86
			CH$_3$CN	94
2	PhCHO	Ph–CH(OH)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	94
			CH$_3$CN	82
3	Ph–CH=CH–CHO	Ph–CH=CH–CH(OH)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	98
			CH$_3$CN	94
4	Ph–CH$_2$CH$_2$–CO–CH$_3$	Ph–CH$_2$CH$_2$–C(CH$_3$)(OH)–CH$_2$–CH=CH$_2$	CH$_2$Cl$_2$	78
5	Ph–CO–CO$_2$Me	Ph–C(CO$_2$Me)(OH)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	87
6	Ph–CH=CH–CO–CH$_3$	Ph–CH=CH–C(CH$_3$)(OH)–CH$_2$–CH=CH$_2$	CH$_2$Cl$_2$	82
7	D-arabinose	[b] AcO–CH$_2$–CH(OAc)–CH(OAc)–CH(OAc)–CH(OAc)–CH(~)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:4)	81[c]
			H$_2$O : EtOH (1:4)	89[d]
			H$_2$O : CH$_3$CN (1:9)	93[e]
8	2-deoxy-D-ribose	[b] AcO–CH$_2$–CH(OAc)–CH(OAc)–CH(OAc)–CH$_2$–CH(~)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	89[f]
9	2-deoxy-D-glucose	[b] AcO–CH$_2$–CH(OAc)–CH(OAc)–CH(OAc)–CH(OAc)–CH$_2$–CH(~)–CH$_2$–CH=CH$_2$	H$_2$O : THF (1:9)	88[f]
10	Ph–CO–CHO·H$_2$O	CH$_2$=CH–CH$_2$–C(Ph)(OH)–CH(OH)–CH$_2$–CH=CH$_2$	CH$_3$CN	78[g]

Table 11. (continued)

Entry	Carbonyl Compound	Product	Solvent	Yield/%
11			H_2O : THF (1:9) CH_3CN	quant. 90
12			H_2O : THF (1:9) CH_3CN	quant. 84
13			CH_3CN	87
14			CH_3CN	90

[a] Carried out at 25 °C except for entries 8 and 9 (60 °C).
[b] The products were isolated after acetlyation.
[c] *syn/anti*=28/72.

[d] *syn/anti*=27/73.
[e] *syn/anti*=26/74.
[f] *syn/anti*=50/50.
[g] Diastereomer ratio=88/12. Relative configuration assignment was not made.

ing homoallylic alcohols in high yields. The reactions were successfully carried out in the presence of a small amount of a surfactant in water without using any organic solvents.

5
Mannich-Type Reactions

5.1
Reactions of Imines with Silyl Enolates

The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of b-amino ketones or esters. Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have been developed [38]. Among them, reactions of imines with enolate components, especially silyl enolates, provide useful and promising methods leading to b-amino ketones or esters. The first report using a stoichiometric amount of $TiCl_4$ as a promoter appeared in 1977 [39], and since then some efficient catalysts have been developed [40].

$$
\underset{R^1}{\overset{N^{R^2}}{\parallel}}H \;+\; \underset{R^4}{\overset{OSiMe_3}{\underset{R^3}{\parallel}}}R^5 \quad\xrightarrow[\text{CH}_2\text{Cl}_2,\ 0\ ^\circ\text{C}]{\begin{array}{c}\text{Ln(OTf)}_3\\(5\ \text{mol}\%)\end{array}}\quad \underset{R^3\ R^4}{\overset{R^2\!-NH\quad O}{R^1}}R^5
$$
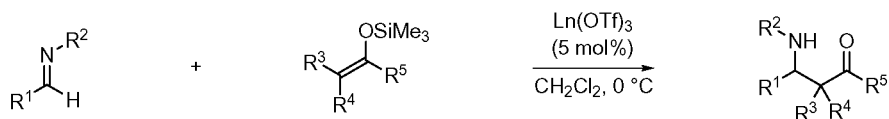
Table 12. Reactions of imines with silyl enolates

Imine	Silyl enolate		Ln	Yield/%
Ph–N=CH–Ph	OSiMe₃ / OMe (isobutenyl)	**3**	Yb	97 [a)]
			Y	81
	OSiMe₃ / SEt		Yb	95
Bn–N=CH–Ph	**3**		Yb	86
			Y	78
	OSiMe₃ / SEt		Yb	65
			Sc	80
	OSiMe₃ / OBn		Yb	80 [b)]
furyl–CH=N–Ph	**3**		Yb	95
	OSiMe₃ / OBn		Yb	67 [c)]
furyl–CH=N–Bn	**3**		Yb	88
Ph–CH=N–Ts	**3**		Yb	88
Ph–C(=O)–CH=N–Ph	**3**		Yb	60
C₄H₉–CH=N–Bn	**3**		Yb	47

[a] Second use=96% yield; third use=98% yield.
[b] *syn/anti*=18/82.
[c] *syn/anti*=21/79.

In aqueous media, water coordinates lanthanide triflates under equilibrium conditions, and thus activation of carbonyl compounds using a catalytic amount of the Lewis acid has been performed. It was expected that, based on the same consideration, the catalytic activation of imines would be possible by using lanthanide triflates.

The reactions of imines with silyl enolates were tested in the presence of 5 mol% of $Ln(OTf)_3$, and selected examples are shown in Table 12 [41]. In most cases the reactions proceeded smoothly in the presence of 5 mol% of $Yb(OTf)_3$ (a representative lanthanide triflate) to afford the corresponding b-amino ester derivatives in good to high yields. Yttrium triflate ($Y(OTf)_3$) was also effective, and the yield was improved when $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$ as a catalyst. Not only silyl enolates derived from esters, but also that derived from a thioester, worked well to give the desired b-amino esters and thioester in high yields. In the reactions of the silyl enolate derived from benzyl propionate, *anti* adducts were obtained in good selectivities. In addition, the catalyst could be recovered after the reaction was completed and could be reused.

5.2
One-Pot Synthesis of β-Amino Esters from Aldehydes

While the Lewis acid-catalyzed reactions of imines with silyl enolates are one of the most efficient methods for the preparation of b-amino esters, many imines are hygroscopic, unstable at high temperatures, and difficult to purify by distillation or column chromatography. It is desirable from a synthetic point of view that imines, generated in situ from aldehydes and amines, immediately react with silyl enolates and provide b-amino esters in a one-pot reaction. However, most Lewis acids cannot be used in this reaction because they decompose or deactivate in the presence of the amines and water that exist during imine formation. Due to the unique properties of $Ln(OTf)_3$, their use as catalysts for the above one-pot preparation of b-amino esters from aldehydes was planned.
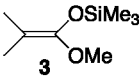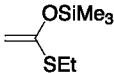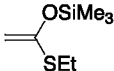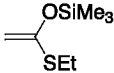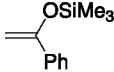
A general scheme of the one-pot synthesis of b-amino esters from aldehydes is shown in Scheme 4 [42]. In the presence of a catalytic amount of $Yb(OTf)_3$ and an additive (a dehydrating reagent such as MS 4 A or $MgSO_4$), an aldehyde was treated with an amine and then with a silyl enolate in the same vessel. Several examples are shown in Tables 13 and 14, and the following characteristic features of this reaction are noted.

1. In every case, b-amino esters were obtained in high yields. Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts.
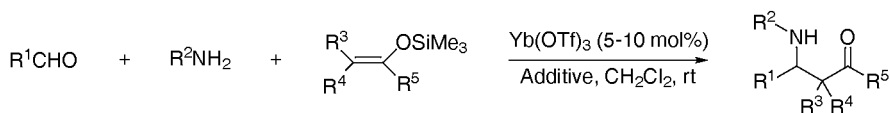
Scheme 4

Table 13. One-pot synthesis of b-amino esters from aldehydes

Entry	R^1	R^2	Silyl enolate	Additive [a]	Yield/%
1	Ph	Ph	![OSiMe3 / OMe, 3]	MS4A MgSO$_4$	90 89
2	Ph	Bn	**3**	MS4A	85
3	Ph	p-MeOPh	**3**	MgSO$_4$	91 [b]
4	Ph	o-MeOPh	**3**	MS4A	96
5	Ph	Ph	OSiMe$_3$ / SEt	MS4A	90
6	Ph	Bn	OSiMe$_3$ / SEt	MS4A	62 [b]
7	Ph	p-MeOPh	OSiMe$_3$ / SEt	MS4A	79 84,[b] 87 [b,c]
8	Ph	C$_4$H$_9$	**3**	MS4A	89
9	PhCO [d]	Ph	**3**	MgSO$_4$	82
10	PhCO [d]	Ph	OSiMe$_3$ / Ph	MgSO$_4$	87
11	PhCH=CH	p-MeOPh	**3**	MgSO$_4$	92 [e]
12	Ph(CH$_2$)$_2$	Bn	**3**	MgSO$_4$	83 [f]
13	C$_4$H$_9$	Bn	**3**	MgSO$_4$	77 [f]
14	C$_8$H$_{17}$	Bn	**3**	MgSO$_4$	81 [f]
15	C$_8$H$_{17}$	Ph$_2$CH	**3**	MgSO$_4$	89 [g]

[a] MS4A or MgSO$_4$ was used. Almost comparable yields were obtained in each case.
[b] CH$_3$CN was used as a solvent.
[c] Sc(OTf)$_3$ was used instead of Yb(OTf)$_3$.
[d] Monohydrate.
[e] C$_2$H$_5$CN, –78 °C.
[f] –78 to 0 °C.
[g] 0 °C.
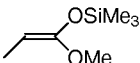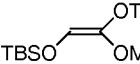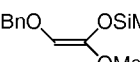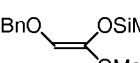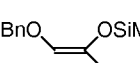
No adducts between aldehydes and the silyl enolates were observed in any reaction.

2. A silyl enol ether derived from a ketone also worked well to afford the b-amino ketone in a high yield (Table 13, entry 10).

3. Aliphatic aldehydes reacted with amines and silyl enolates to give the corresponding b-amino esters in high yields. In some reactions of imines, it is known that aliphatic enolizable imines prepared from aliphatic aldehydes gave poor results.

$$R^1CHO \quad + \quad R^2NH_2 \quad + \quad \underset{R^4}{\overset{R^3}{\diagup}}\!\!-\!OSiMe_3 \quad \xrightarrow[\text{MS4A, } C_2H_5CN, \, -78\,°C]{\text{Yb(OTf)}_3 \text{ (5-10 mol\%)}} \quad \underset{R^1}{\overset{R^2\diagdown NH}{\diagup}}\underset{R^3}{\diagup}\overset{O}{\diagdown}R^4$$
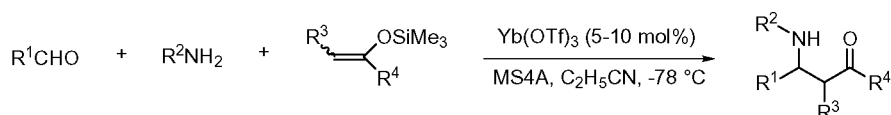
Table 14. Diastereoselective one-pot synthesis of b-amino esters from aldehydes

Entry	R^1	R^2	Silyl enolate	Yield/%	*syn / anti* [a]
1	Ph	Bn	OSiMe₃ / OMe	90	1 / 13.3
2	Ph	Bn	OTBS, TBSO, OMe	78	1 / 9.0
3	Ph(CH₂)₂	Ph₂CH	BnO, OSiMe₃, OMe	88	8.1 / 1
4	C₄H₉	Ph₂CH	BnO, OSiMe₃, OMe	90	8.1 / 1
5	(CH₃)₂CHCH₂	Ph₂CH	BnO, OSiMe₃, OMe	86	7.3 / 1

[a] Determined by [1]H NMR analysis.

4. Phenylglyoxal monohydrate also worked well in this reaction. The imine derived from phenylglyoxal is unstable and a troublesome treatment is known to be required for its use [43].

5. The catalyst could be recovered after the reaction was completed and could be reused (first run, 91%; second run, 92%, in the reaction of benzaldehyde, *p*-anisidine, and silyl enolate **3** (Table 13, entry 3)).

6. As for the diastereoselectivity of this reaction, good results were obtained after examination of the reaction conditions. While *anti* adducts were produced preferentially in the reactions of benzaldehyde, *syn* adducts were obtained with high selectivities in the reactions of aliphatic aldehydes (Table 14).

7. The high yields of the present one-pot reactions depend on the unique properties of $Ln(OTf)_3$ as the Lewis acid catalysts. Although $TiCl_4$ and TMSOTf are known to be effective for the activation of imines [39,44], the use of even stoichiometric amounts of $TiCl_4$ and TMSOTf instead of $Ln(OTf)_3$ in the present one-pot reactions gave only trace amounts of the product in both cases (Table 15).

8. One-pot preparation of a b-lactam from an aldehyde, an amine, and a silyl enolate has been achieved based on the present reaction (Scheme 5). The reaction of the aldehyde, the amine, and **2** was carried out under the standard conditions, and $Hg(OCOCF_3)_2$ was then added to the same pot. The desired b-lactam was isolated in a 78% yield.

$C_8H_{17}CHO$ + Ph_2CHNH_2 +   [ketene silyl acetal structure with OSiMe₃ and OMe, labeled **3**]

Activator
→
$MgSO_4$
CH_2Cl_2, 0 °C

[product structure: Ph₂CH–NH, C_8H_{17}, O, OMe]
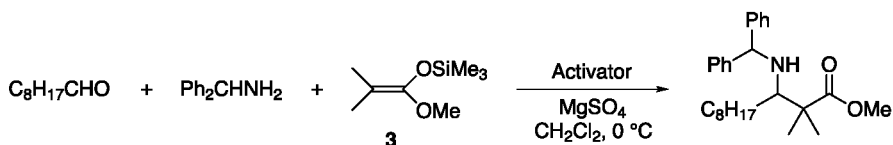
Table 15. Effect of catalysts

Entry	Activator		Yield/%
1	Yb(OTf)$_3$	10 mol%	89
2	TiCl$_4$	100 mol%	trace
3	TMSOTf	100 mol%	trace

PhCHO   +   p-MeOPhNH$_2$ +   [ketene silyl acetal with OSiMe₃ and SEt]

1. Yb(OTf)$_3$ (10 mol%)
   MS4A
→
2. Hg(OCOCF$_3$)$_2$
   78%

[β-lactam product: p-MeOPh–N, O, Ph]
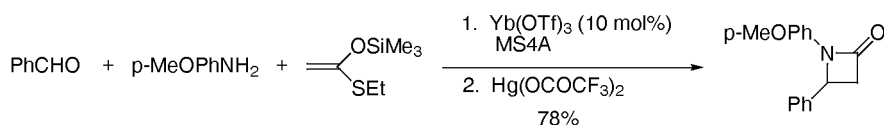
Scheme 5

Thus, the one-pot synthesis of b-amino esters from aldehydes has been achieved by using lanthanide triflate catalysis. The high efficiency using simple starting materials and a catalytic amount of a reusable catalyst is especially noteworthy.

5.3
Use of Acylhydrazones as Electrophiles in Mannich-Type Reactions

Hydrazones are aldehyde and ketone equivalents as well as imines. Their stability is much higher than imines and actually hydrazones derived from aliphatic aldehydes are often crystalline and can be isolated and stored at room temperature. However, their reactivity as electrophiles is known to be low, and there have been many fewer reports on the reactions of hydrazones with nucleophiles than those of imines [45, 46].

While 3-phenylpropionaldehyde phenylhydrazone did not react with ketene silyl acetal **3b** (R^2=tBu) derived from methyl isobutyrate at all, 3-phenylpropionaldehyde acylhydrazones reacted with **3b** in the presence of a catalytic amount of Sc(OTf)$_3$. Among the acylhydrazones tested, 4-trifluoromethylbenzoylhydrazone (**4a**, R^1=CF$_3$) gave the best yield (Table 16). It is noteworthy that the electronic effect of the benzoyl moieties influenced the yields dramatically. While hydrazones with electron-donating groups gave lower yields, higher yields were
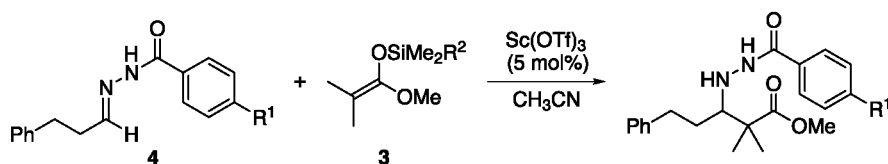
Table 16. Effect of R^1 and Lewis acids

Entry	Lewis Acid	R^1	R^2	Temp/°C	Yield/%
1	Sc(OTf)$_3$	H	^{t}Bu	-20	37
2	Sc(OTf)$_3$	MeO	^{t}Bu	-20	7
3	Sc(OTf)$_3$	NO$_2$	^{t}Bu	-20	77
4	Sc(OTf)$_3$	CF$_3$	^{t}Bu	-20	88
5	Sc(OTf)$_3$	CF$_3$	Me	-20	97 (75[a,b])
6	BF$_3$·OEt$_2$	CF$_3$	Me	0	4[a]
7	TiCl$_4$	CF$_3$	Me	0	13[a]
8	SnCl$_4$	CF$_3$	Me	0	46[a]

[a] Dichloromethane was used as a solvent.
[b] 0 °C.

obtained using hydrazones with electron-withdrawing groups. As for Lewis acids, Sc(OTf)$_3$ gave an excellent yield [47–49], and much lower yields were obtained by using typical Lewis acids such as TiCl$_4$, SnCl$_4$, and BF$_3$.OEt$_2$ [50].

Several examples of the reactions of 4-trifluoromethylbenzoylhydrazones with silyl enolates are shown in Table 17. Hydrazones derived from aromatic, aliphatic, and a,b-unsaturated aldehydes reacted with silyl enolates smoothly to afford the corresponding b-N'-acylhydrazinocarbonyl compounds in high yields. It is noted that several aliphatic hydrazones, readily prepared from aliphatic aldehydes, reacted with silyl enolates smoothly to afford the corresponding adducts in high yields [51]. All aliphatic acylhydrazones tested were crystalline and could be stored at room temperature. As for silyl enolates, the enolates derived from both esters and thioesters worked well. 1-Phenyl-1-trimethylsiloxyethene (a ketone-derived silyl enolate) also reacted with an aliphatic acylhydrazone to afford the corresponding adduct in a good yield.

Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compound (6a) was successfully carried out using Raney Ni under H$_2$ atmosphere (Scheme 6) [52]. Thus, adduct 5 was treated with a catalytic amount of Raney Ni (W-3) under H$_2$ (1 atm) at ambient temperature. After cleavage of the nitrogen-nitrogen bond, the resulting amine was protected as its t-butoxycarbonyl (Boc) group (6). It was found that b-lactam 7 was obtained by treatment of 5 with n-BuLi at –78 °C [53], while pyrazolone 8 was produced in the presence of NaOMe
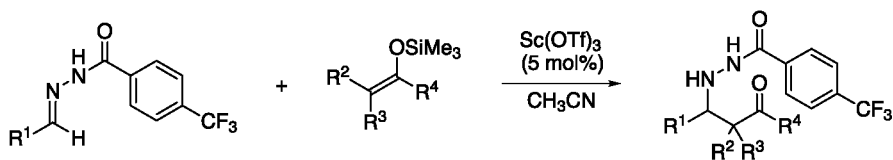
Table 17. Reactions of acylhydrazones with silyl enolates

Entry	R^1	R^2	R^3	R^4	Temp/°C	Yield/%
1	Ph(CH$_2$)$_2$	Me	Me	OMe	-20	97
2	(CH$_3$)$_2$CHCH$_2$	Me	Me	OMe	rt	88
3	CH$_3$(CH$_2$)$_5$	Me	Me	OMe	0	95
4	Ph	Me	Me	OMe	rt	73
5	CH$_3$CH=CH	Me	Me	OMe	0-rt	80
6	PhCH=CH	Me	Me	OMe	rt	75
7	Ph(CH$_2$)$_2$	H	H	SEt	0	79
8	CH$_3$(CH$_2$)$_5$	H	H	SEt	0	80
9	(CH$_3$)$_2$CHCH$_2$	H	H	SEt	0-rt	68
10	c-C$_6$H$_{11}$	H	H	SEt	0	68
11	(CH$_3$)$_2$CHCH$_2$	Me	Me	SEt	0-rt	83
12	Ph(CH$_2$)$_2$	OBn	H	O^{i}Pr	-78	90[a,b]
13	Ph(CH$_2$)$_2$	H	Me	OPh	-45-0	95[a,c]
14	Ph(CH$_2$)$_2$	H	H	Ph	rt	66

[a] Propionitrile was used as a solvent.
[b] *syn/anti*=75/25.
[c] *syn/anti*=64/36.
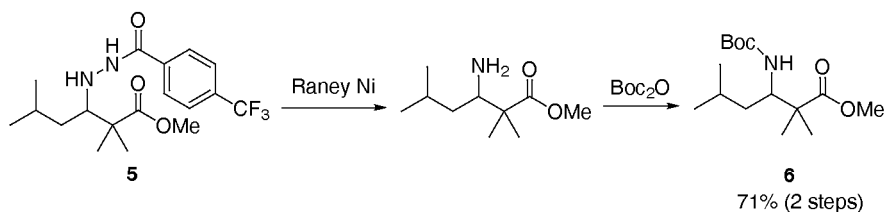
Scheme 6

at 70°C (Scheme 7). Since isomerization from **7** to **8** was observed under these conditions (NaOMe), **7** and **8** were expected to be kinetic and thermodynamic products, respectively. Moreover, pyrazolidinone **9** was obtained in the presence of samarium diiodide (SmI$_2$) [54] in THF-MeOH at 45°C.
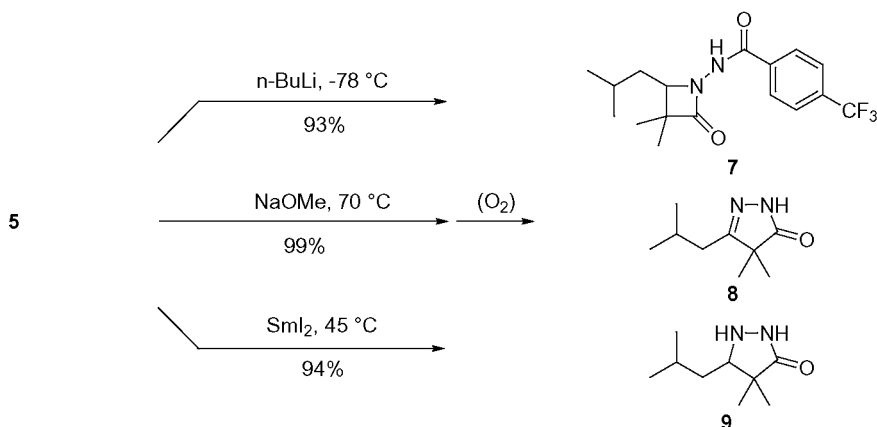
Scheme 7

5.4
Aqueous Mannich-Type Reaction

As mentioned in the previous sections, silyl enolates are excellent enolate components in the Mannich-type reactions with imines. Alternatively, it was found that vinyl ethers also reacted with imines smoothly in the presence of a catalytic amount of $Ln(OTf)_3$ to afford the corresponding b-amino ketones. In addition, the reactions proceeded smoothly by the combination of aldehydes, amines, and vinyl ethers in aqueous media [55].

A general scheme for the new Mannich-type reaction is shown below (Scheme 8); the procedure is very simple. In the presence of 10 mol% of $Yb(OTf)_3$, an aldehyde, an amine, and a vinyl ether were combined in a solution of THF-water (9:1) at room temperature to afford a b-amino ketone.

Selected examples of the present reaction are shown in Table 18. In all cases, b-amino ketones were obtained in good yields. Several characteristic features are noteworthy in this reaction. The procedure is very simple, consisting of simply mixing an aldehyde, an amine, a vinyl ether, and a small amount of $Ln(OTf)_3$ in aqueous solution. The catalyst could be recovered after the reaction was completed and could be reused (first run, 93%; second run, 83%; third run, 87%, in the reaction of phenylglyoxal·monohydrate, p-chloroaniline, and 2-methoxypropene). Commercially available formaldehyde and chloroacetaldehyde water solutions were used directly and the corresponding b-amino ketones were obtained in good yields. Phenylglyoxal·monohydrate, methyl glyoxylate, an aliphatic aldehyde, and an a,b-unsaturated ketone also worked well to give the corresponding b-amino esters in high yields. In some Mannich reactions with preformed iminium salts and imines, it is known that yields are often low because of the instability of the imines derived from these aldehydes or troublesome treatments are known to be required for their use [43, 56].

$$R^1CHO \quad + \quad R^2NH_2 \quad + \quad \overset{OMe}{\underset{R^3}{\diagup}} \quad \xrightarrow[\text{THF - H}_2\text{O (9:1)}]{\text{Yb(OTf)}_3(10 \text{ mol\%})} \quad \overset{R^2}{\underset{R^1}{\diagdown}} \overset{NH}{} \overset{O}{\underset{R^3}{\diagup}}$$
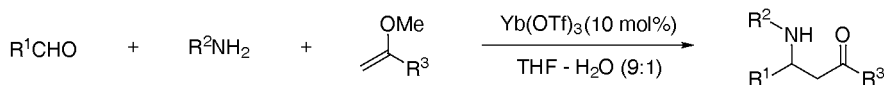
Scheme 8

Table 18. Synthesis of b-amino ketones in aqueous media

R^1	R^2	R^3	Yield/%
H	p-ClPh	Me	92
H	p-Ans	Me	76
H	p-Ans	Ph	quant.
Ph	p-ClPh	Me	90
Ph	p-Ans	Me	74
Ph(CH$_2$)$_2$	p-ClPh	Me	55
ClCH$_2$	p-ClPh	Me	59
PhCH=CH	p-ClPh	Me	73
PhCO	p-ClPh	Me	93
PhCO	Ph	Me	90
PhCO	p-Ans	Me	75
PhCO	p-Ans	Ph	85
MeO$_2$C	p-Ans	Me	67
MeO$_2$C	p-Ans	Ph	58

p-Ans=*p*-Anisidine

$$R^1CHO \xrightleftharpoons[-H_2O]{R^2NH_2} \underset{R^1 \diagdown H}{\overset{N \diagup R^2}{\|}} \overset{OMe}{\underset{R^3}{\diagup}} \quad \underset{R^1}{\overset{R^2}{\diagdown}}N^- \overset{OMe}{\underset{+ \, R^3}{\diagdown}} \xrightarrow{H_2O} \left[\underset{R^1}{\overset{R^2}{\diagdown}}\overset{NH}{} \overset{OMe}{\underset{R^3}{\overset{OH}{\diagdown}}} \right] \longrightarrow \underset{R^1}{\overset{R^2}{\diagdown}}\overset{NH}{} \overset{O}{\underset{R^3}{\diagup}}$$
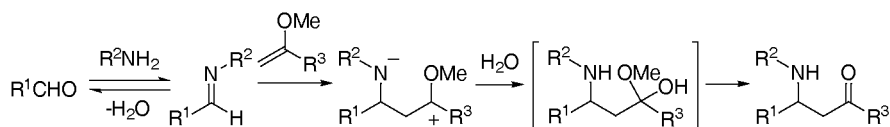
Scheme 9

A possible mechanism for the present reaction is shown in Scheme 9. It should be noted that dehydration accompanied by imine formation and successive addition of a vinyl ether proceed smoothly in aqueous solution and that the first aqueous Mannich-type reaction catalyzed by Ln(OTf)$_3$ has been developed [57]. Use of Ln(OTf)$_3$, a water-tolerant Lewis acid, is key and essential in this reaction.

6
Aza Diels-Alder Reactions

6.1
Reactions of Imines with Dienes or Alkenes

The imino Diels-Alder reaction is among the most powerful synthetic tools for constructing N-containing six-membered heterocycles, such as pyridines and quinolines [58]. Although Lewis acids often promote these reactions, more than stoichiometric amounts of the acids are required due to the strong coordination of the acids to nitrogen atoms [58]. Use of $Ln(OTf)_3$ as a catalyst was investigated in this reaction.
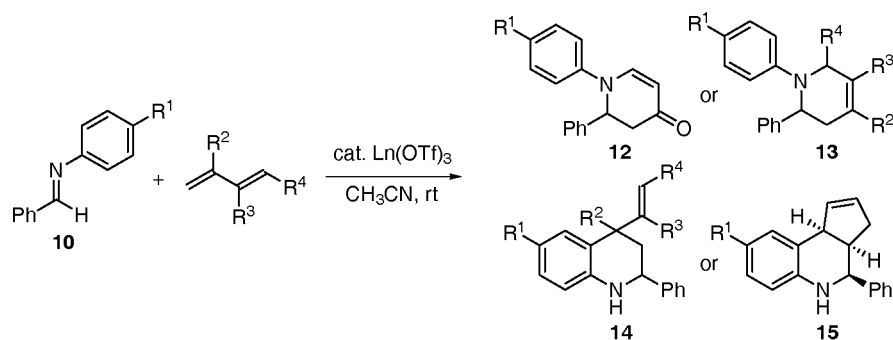
Table 19. Syntheses of pyridine dereivatives catalyzed by $Ln(OTf)_3$

R^1	Diene	$Ln(OTf)_3$ (mol%)	Product	Yield/%
H (10a)	OSiMe$_3$	Yb(OTf)$_3$ (10)	12a	93 (99)[a]
OMe (10b)	OMe		12b	82
Cl (10c)	11		12c	92
H (10a)		Sc(OTf)$_3$ (20)	13a+14a	54[b]
OMe (10b)			13b+14b	71[c]
Cl (10c)			13c+14c	50[d]
H (10a)		Yb(OTf)$_3$ (10)	15a	69 (91)[e,f]
OMe (10b)			15b	38[f]
Cl (10c)			15c	85[f]

[a] 10 mol% Sc(OTf)$_3$ was used. The reaction was carried out at 0 °C.
[b] **13a** 37%, **14a** 17%.
[c] **13b** 8%, **14b** 63%.
[d] **13c** 37%, **14c** 13%.
[e] 20 mol% Sc(OTf)$_3$ was used.
[f] cis/trans=94/6.
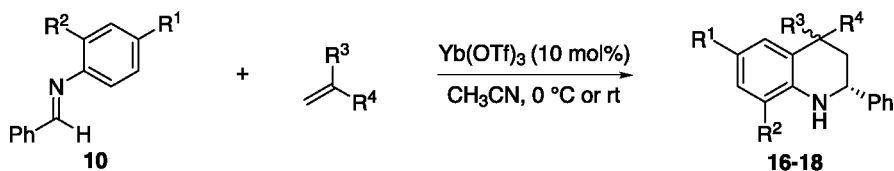
Table 20. Syntheses of quinoline derivatives catalyzed by $Ln(OTf)_3$

R^1	R^2		Alkene	Product	Yield/%	*cis/trans*
H	H	**(10A)**		**16A**	75	57/43
OMe	H	**(10B)**		**16B**	0	—
Cl	H	**(10C)**	SPh	**16C**	quant.	nd[a]
H	OMe	**(10D)**		**16D**	70	nd[a]
H	H	**(10A)**		**17A**	96	nd[a]
OMe	H	**(10B)**	OEt	**17B**	77	67/33
Cl	H	**(10C)**		**17C**	95	nd[a]
OMe	H	**(10B)**	Ph ⟍ OSiMe₃	**18**	quant.	83/17[b]

[a] Not determined.
[b] Relative configuration assignment was not made.

In the presence of 10 mol% of ytterbium triflate ($Yb(OTf)_3$, a representative lanthanide triflate), *N*-benzylideneaniline (**10a**) was treated with 2-trimethylsiloxy-4-methoxy-1,3-butadiene (Danishefsky's diene, **11**) [59] in acetonitrile at room temperature. The imino Diels-Alder reaction proceeded smoothly to afford the corresponding tetrahydropyridine derivative in a 93% yield (Table 19). The adduct was obtained quantitatively when $Sc(OTf)_3$ was used as a catalyst. Imines **10b** and **10c** also reacted smoothly with **11** to give the corresponding adducts in high yields. The reaction of **10a** with cyclopentadiene was performed under the same reaction conditions. It was found that the reaction course changed in this case and that a tetrahydroquinoline derivative was obtained in a 69% yield. In this reaction, the imine worked as an azadiene toward one of the double bonds of cyclopentadiene as a dienophile [43, 60]. In the reactions of 2,3-dimethylbutadiene, mixtures of tetrahydropyridine and tetrahydroquinoline derivatives were obtained.

Other examples and effects of $Ln(OTf)_3$ are shown in Tables 20 and 21, respectively [61]. A vinyl sulfide, a vinyl ether, and a silyl enol ether worked well as dienophiles to afford tetrahydroquinoline derivatives in high yields [62, 63]. As for the $Ln(OTf)_3$, heavy lanthanides such as Er, Tm, and Yb gave better results.
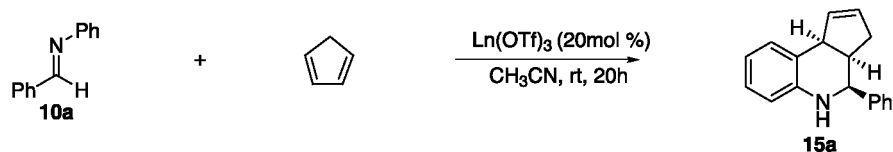
Table 21. Effects of $Ln(OTf)_3$ (1)

Ln	Yield/%
Sc	94
Y	60
La	45
Pr	57
Nd	60
Sm	63
Eu	63
Gd	76
Dy	63
Ho	64
Er	97
Tm	92
Yb	85
Lu	72
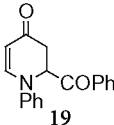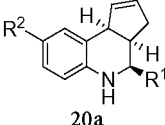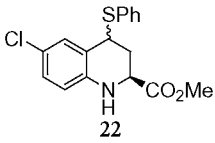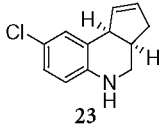
6.2
Three-Components Coupling Reactions of Aldehydes, Amines, and Dienes or Alkenes

One synthetic problem in the imino Diels-Alder reactions is the imines' stability under the influence of Lewis acids. It is desirable that the imines activated by Lewis acids are immediately trapped by dienes or dienophiles [57]. In 1989, Sisko and Weinreb reported a convenient procedure for the imino Diels-Alder reaction of an aldehyde and a 1,3-diene with N-sulfinyl p-toluenesulfonamide via N-sulfonyl imine produced in situ, by using a stoichiometric amount of $BF_3.OEt_2$ as a promoter [64].

Bearing in mind the usefulness and efficiency of one-pot procedures, three-component coupling reactions between aldehydes, amines, and alkenes via imine formation and imino Diels-Alder reactions were examined by using $Ln(OTf)_3$ as a catalyst.

In the presence of 10 mol% of ytterbium triflate and magnesium sulfate, benzaldehyde was treated with aniline and 11 successively in acetonitrile at room

$$R^1CHO \quad + \quad \underset{H_2N}{\overset{R^2}{\bigcirc}} \quad + \quad \text{diene or alkene} \quad \xrightarrow[\text{CH}_3\text{CN, rt}]{\begin{array}{c}\text{Yb(OTf)}_3\\(5\text{-}20\text{ mol\%})\end{array}} \quad \begin{array}{c}\text{pyridine or quinoline}\\\text{derivatives}\end{array}$$
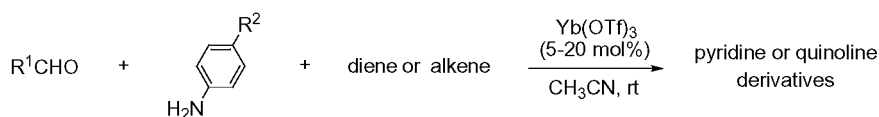
Table 22. One-pot synthesis of pyridine and quinoline derivatives

R^1	R^2	Diene or Alkene	Product	Yield/%	*cis/trans*
Ph	H	**11**	**12a**	80 (83)[a]	—
		(cyclopentadiene)	**15a**	56	94/ 6
		SPh-vinyl	**16a**	70	nd[b]
	Cl		**16c**	quant.	nd[b]
	H	OEt-vinyl	**17a**	60	79/21
PhCO	H	**11**	**19**	76	—
	H	(cyclopentadiene)	**20a**	94 (97)[c]	96/ 4 (96/ 4)
	OMe		**20b**	94	94/ 6
	Cl		**20c**	quant.	96/ 4
MeO$_2$C	H		**21a**	82	99/ 1
	Cl		**21c**	84	99/ 1
	Cl	SPh-vinyl	**22**	65	nd[b]
H[d]	Cl	(cyclopentadiene)	**23**	90[c]	—

[a] Sc(OTf)$_3$ (10 mol%) was used.
[b] Not determined.
[c] The reactions were carried out in aqueous solution (H$_2$O:EtOH:toluene=1:9:4).
[d] Commercial formaldehyde water solution was used.
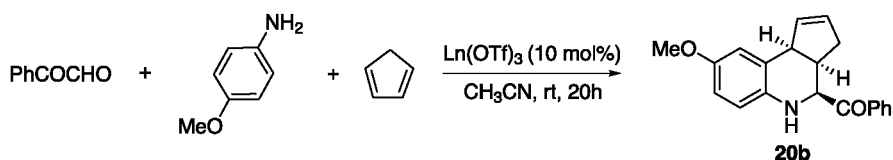
Table 23. Effects of $Ln(OTf)_3$ (2)

Ln	Yield/%
Sc	63
Y	77
La	88
Pr	75
Nd	97
Sm	91
Eu	87
Gd	91
Dy	87
Ho	76
Er	84
Tm	84
Yb	94
Lu	80

temperature. The three-component coupling reaction proceeded smoothly to afford the corresponding tetrahydropyridine derivative in an 80% yield. It is noteworthy that $Yb(OTf)_3$ kept its activity and effectively catalyzed the reaction even in the presence of water and the amine [65]. Use of $Sc(OTf)_3$ slightly improved the yield. Other examples of the three-component coupling reaction are shown in Table 22. In the reaction between benzaldehyde, anisidine, and cyclopentadiene under the same reaction conditions, the reaction course changed and the tetrahydroquinoline derivative was obtained in a 56% yield. A vinyl sulfide, a vinyl ether, and a silyl enol ether worked well as dienophiles to afford tetrahydroquinoline derivatives in high yields. Phenylglyoxal monohydrate reacted with amines and **11** or cyclopentadiene to give the corresponding tetrahydropyridine or quinoline derivatives in high yields. As mentioned in the previous section, the imine derived from phenylglyoxal is known to be highly hygroscopic and its purification by distillation or chromatography is very difficult due to its instability

[43]. Moreover, the three-component coupling reactions proceeded smoothly in aqueous solution, and commercial formaldehyde water solution could be used directly. Most lanthanide triflates tested were effective in the three-component coupling reactions (Table 23). These reactions provide very useful routes for the synthesis of pyridine and quinoline derivatives.

6.3
Reaction Mechanism

In the reactions of **10a–10c** with cyclopentadiene, a vinyl sulfide, or a vinyl ether (**10a–c** work as azadienes), **10c** gave the best yields, while the yields using **10b** were lowest. The HOMO and LUMO energies and coefficients of **10a–c** and protonated **10a–c** are summarized in Table 24. These data do not correspond to the differences in reactivity between **10a–c** if the reactions are postulated to proceed via concerted [4+2] cycloaddition. On the other hand, the high reactivity of **4c** toward electrophiles compared to **10a** and **10b** may be accepted by assuming a stepwise mechanism.

The reaction of **10a** with 2-methoxypropene was tested in the presence of Yb(OTf)$_3$ (10 mol%). The main product was tetrahydroquinoline derivative **24a**, and small amounts of quinoline **25a** and b-amino ketone dimethylacetal **26a** were also obtained (Eq. 5). On the other hand, the three components coupling reaction between benzaldehyde, aniline, and 2-methoxypropene gave only a small amount of tetrahydroquinoline derivative **24a**, and the main products in this case were b-amino ketone **27a** and its dimethylacetal **26a** (Eq. 6). Similar results were obtained in the reaction of **4b** with 2-methoxypropene and the three
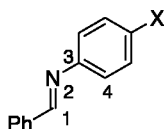
Table 24. HOMO and LUMO energies and coefficient of **10a–c**[a]

	HOMO	Coefficient			HOMO	Coefficient			
	/eV	C1	N2	C3	C4	/eV	C1	N2	C3	C4
10a	-8.97	0.32	0.35	-0.34	-0.24	-0.69	0.43	-0.38	-0.30	0.27
10b	-8.68	0.32	0.29	-0.40	-0.24	-0.64	0.43	-0.38	-0.28	0.28
10c	-8.93	0.30	0.31	-0.35	-0.22	-0.85	0.43	-0.35	-0.33	0.27
10a - H+	-13.19| 0.15	0.31	-0.39	-0.19	-5.75	0.63	-0.48	-0.09	0.21
10b - H+	-12.53| 0.20	0.18	-0.46	-0.08	-5.58	0.62	-0.49	-0.07	0.21
10c - H+	-12.58| 0.16	0.15	-0.37	-0.10	-5.77	0.63	-0.47	-0.19	0.21

[a] Calculated with MOPAC Ver. 6.01 using the PM3 Hamiltonian. MOPAC Ver. 7: Stewart JJP (1989) QCPE Bull 10:9. Revised as Ver. 6.01 by Tsuneo Hirano, University of Tokyo, for HI-TAC and UNIX machines (1989) JCPE Newslett 10:1.
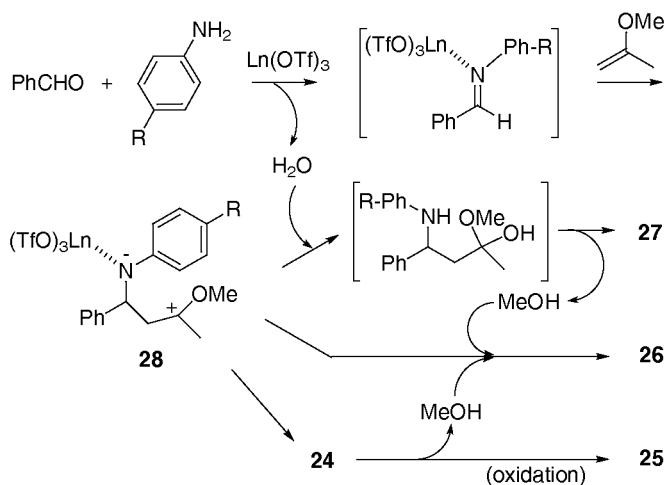
Scheme 10

components coupling reaction between benzaldehyde, anisidine, and 2-methoxypropene (Eqs. 7 and 8).

A possible mechanism of these reactions is shown in Scheme 10. Intermediate 28 is quenched by water and methanol generated in situ to afford 26 and 27, respectively. While 24 is predominantly formed from 28 under anhydrous conditions, formation of 26 and 27 predominated in the presence of even a small amount of water. It is noted that these results suggest a stepwise mechanism in these types of imino Diels-Alder reactions [66].

$$(5)$$

$$(6)$$

$$(7)$$

PMP = *p*-MeO-Ph

$$\text{PhCHO} \ + \ \text{(aryl amine)} \ + \ \text{(enol ether)} \ \xrightarrow[\text{MgSO}_4, \text{CH}_3\text{CN, rt}]{\text{Yb(OTf)}_3 \, (10 \text{ mol\%})} \ \textbf{26b} \ + \ \textbf{27b} \qquad (8)$$
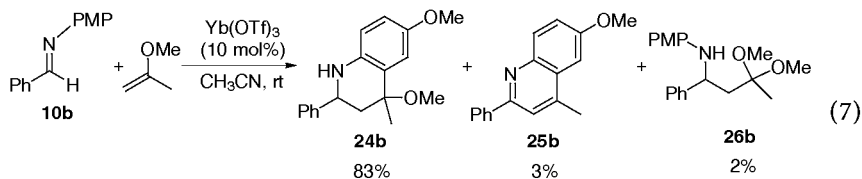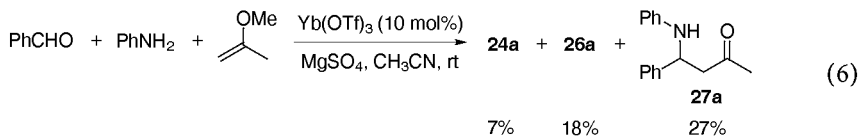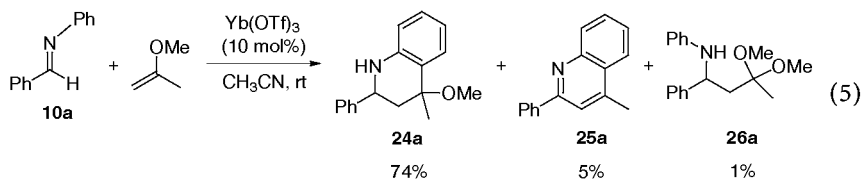
PMP = p-MeO-Ph   34%   37%
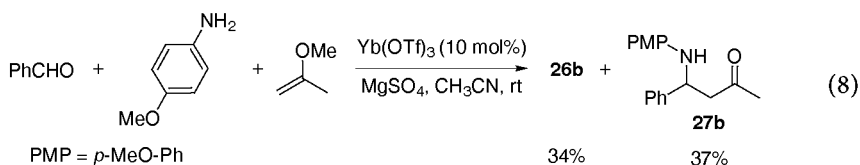
Thus, a new type of Lewis acid, lanthanide triflates, is quite effective for the catalytic activation of imines, and has achieved imino Diels-Alder reactions of imines with dienes or alkenes. The unique reactivities of imines which work as both dienophiles and azadienes under certain conditions were also revealed. Three-component coupling reactions between aldehydes, amines, and dienes or alkenes were successfully carried out by using Ln(OTf)_3 as catalysts to afford pyridine and quinoline derivatives in high yields. The triflates were stable and kept their activity even in the presence of water and amines. According to these reactions, many substituted pyridines and quinolines can be prepared directly from aldehydes, amines, and dienes or alkenes. A stepwise reaction mechanism in these reactions was suggested from the experimental results.

7
Asymmetric Diels-Alder Reactions

Recently, some efficient asymmetric Diels-Alder reactions catalyzed by chiral Lewis acids have been reported [67]. The chiral Lewis acids employed in these reactions are generally based on traditional acids such as titanium, boron, or aluminum reagents, and they are well modified to realize high enantioselectivities. Although lanthanide compounds were expected to be Lewis acid reagents, only a few asymmetric reactions catalyzed by chiral lanthanide Lewis acids were reported. Pioneering work by Danishefsky et al. demonstrated that Eu(hfc)_3 (an NMR shift reagent) catalyzed hetero-Diels-Alder reactions of aldehydes with siloxydienes, but enantiomeric excesses were moderate [68].

As shown in the previous section, lanthanide triflates were found to be good catalysts in the Diels-Alder reaction of various dienophiles with cyclic and acyclic dienes. The reactions proceeded smoothly in the presence of a catalytic amount of the triflate to give the corresponding adducts in high yields. Moreover, the catalyst was stable in water and was easily recovered from the aqueous layer after the reaction was completed, and could be reused. These unique properties were considered to be dependent on the specific characters of the lanthanides(III) [69], and design of chiral lanthanide triflates which could work as an efficient catalyst in the asymmetric Diels-Alder reaction was performed.

First, Yb(OTf)_3 was chosen as a representative of the lanthanide triflates. The chiral Yb triflate was prepared in situ from Yb(OTf)_3, (R)-(+)-binaphthol, and a

tertiary amine (Eq. 9) [70], and a model reaction of 3-(2-butenoyl)-1,3-oxazoli-din-2-one (**6**) with cyclopentadiene was examined [71].

$$Yb(OTf)_3 \quad \xrightarrow[\text{MS 4A}]{\begin{array}{c}1.2 \text{ eq} \\ \text{(binaphthol-OH, OH)}\end{array}} \quad \xrightarrow[\text{0 °C, 30 min}]{2.4 \text{ eq. amine}} \quad \text{"chiral Yb triflate"} \qquad (9)$$
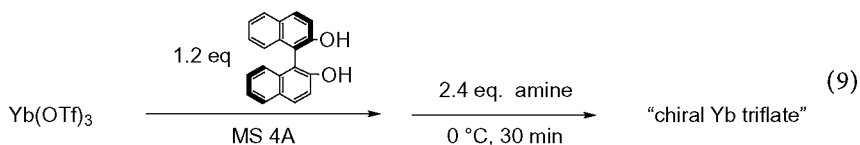
Thus, in the presence of a chiral Yb triflate prepared from $Yb(OTf)_3$, (R)-(+)-binaphthol, and triethylamine at 0 °C for 0.5 h in dichloromethane, **29** reacted with cyclopentadiene at room temperature to afford the Diels-Alder adduct in an 87% yield (*endo/exo*=76/24) and the enantiomeric excess of the *endo* adduct was shown to be 33%. After screening several reaction conditions, it was found that the amine employed at the stage of the preparation of the chiral ytterbium triflate strongly influenced the diastereo- and enantioselectivities. In general, bulky amines gave better results and 70%, 75%, and 71% ees were observed when diisopropylethylamine, *cis*-2,6-dimethylpiperidine, and *cis*-1,2,6-trimeth-ylpiperidine were used, respectively. In addition, a better result was obtained when the amine was combined with molecular sieves 4 Å (*cis*-1,2,6-trimethyl-piperidine, 91% yield, *endo/exo*=86/14, *endo*=90% ee), and the enantiomeric excess was further improved to 95% when the reaction was carried out at 0 °C [72].

At this stage, although the reaction conditions were optimized, aging of the catalyst was found to take place. High selectivities (77% yield, *endo/exo*=89/11, *endo*=95% ee) were obtained when the diene and the dienophile were added just after $Yb(OTf)_3$, (R)-(+)-binaphthol, and a tertiary amine were stirred at 0 °C for 0.5 h in dichloromethane (the original catalyst system). On the other hand, the selectivities became lower in accordance with the stirring time of the catalyst so-lution and the temperature. These results seemed to be ascribed to the aging of the catalyst, but the best result (77% yield, *endo/exo*=89/11, *endo*=95% ee) was obtained when the mixture (the substrates and 20 mol% of the catalyst) was stirred at 0 °C for 20 h. It was suggested from this result that the substrates or the product stabilized the catalyst. The effect of the substrates or the product on the stabilization of the catalyst was then examined, and the dienophile (**29**) was found to be effective in preventing the catalyst from aging. When 20 mol% of the original catalyst system and **29** (additive) were stirred at 0 °C for 5.5 h in dichlo-romethane, the product was obtained in a 66% yield, *endo/exo*=87/13, and the enantiomeric excess of the *endo* adduct was 88%.

Moreover, after screening several additives other than **29**, it was found that some additives were effective not only in stabilizing the catalyst but also *in con-trolling the enantiofacial selectivities in the Diels-Alder reaction*. Selected exam-ples are shown in Table 25. When 3-acetyl-1,3-oxazolidin-2-one (**30**) was com-bined with the original catalyst system (to form catalyst A), the *endo* adduct was
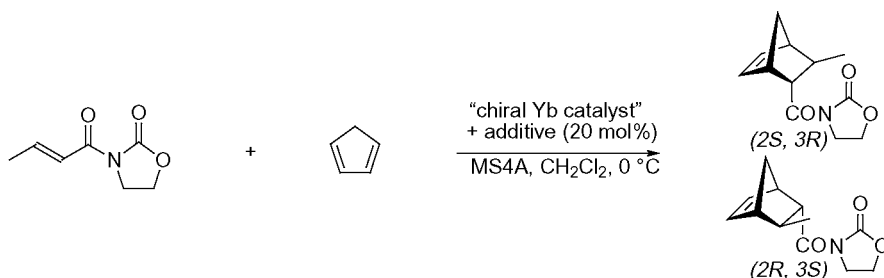
Table 25. Effect of additives
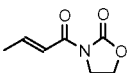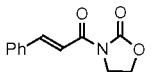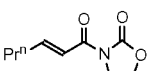
Additive	Yield/%	endo/exo	2S,3R/2R,3S	(ee (%))[a]
29	66	87/13	**94.0**/ 6.0	(88)
30	77	89/11	**96.5**/ 3.5	(93)
	80	88/12	22.5/**77.5**	(55)
	36	81/19	19.0/**81.0**	(62)
	69	88/12	15.5/**84.5**	(69)
Ph	83	93/ 7	9.5/**90.5**	(81)[b]
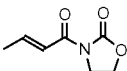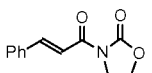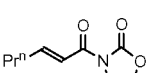
[a] Enantiomer ratios of endo adducts.
[b] 1,2,2,6,6-Pentamethylpiperidine was used instead of cis-1,2,6-trimethylpiperidine.
Yb(OTf)$_3$, MS4A, and the additive were stirred in dichloromethane at 40 °C for 3 h.

obtained in 93% ee and the absolute configuration of the product was *2 S, 3R*. On the other hand, when acetyl acetone derivatives were mixed with the catalyst, *reverse enantiofacial selectivities were observed*. The *endo* adduct with an absolute configuration of *2R, 3S* was obtained in 81% ee when 3-phenylacetylacetone (PAA) was used as an additive (catalyst B). In these cases, the chiral source was the same (*R*)-(+)-binaphthol. Therefore, *the enantioselectivities were controlled by the achiral ligands, 3-acetyl-1,3-oxazolidin-2-one and PAA* [73].

As shown in Table 26, the same selectivities were observed in the reactions of other 3-acyl-1,3-oxazolidin-2-ones. Thus, by using the same chiral source ((*R*)-(+)-binaphthol), both enantiomers of the Diels-Alder adducts between 3-acyl-1,3-oxazolidin-2-ones and cyclopentadiene were prepared. Traditional methods have required both enantiomers of chiral sources in order to prepare both enantiomers stereoselectively [74], but the counterparts of some chiral sources are of poor quality or are hard to obtain (for example, sugars, amino acids, alkaloids, etc.). *It is noted that the chiral catalysts with reverse enantiofacial selectivities could be prepared by using the same chiral source and a choice of achiral ligands.*

Table 26. Synthesis of both enantiomers of the Diels-Alder adducts between cyclopentadiene and dienophiles by use of catalysts A and B

Dienophile	Catalyst A			
	Yield/%	endo/exo	2S,3R/2R,3S	(ee (%))[b]
	77	89/11	**96.5**/ 3.5	(93)
	77	89/11	**97.5**/ 2.5	(95)[c]
	40	81/19	**91.5**/ 8.5[d]	(83)
	34	80/20	**93.0**/ 7.0	(86)
	81	80/20	**91.5**/ 8.5	(83)[c]

Dienophile	Catalyst B[a]			
	Yield/%	endo/exo	2S,3R/2R,3S	(ee (%))[b]
	83	93/ 7	9.5/**90.5**	(81)
	60	89/11	10.5/**89.5**[d]	(79)
	51	89/11	8.5/**91.5**[d]	(83)
	51	89/11	5.5/**94.5**[d]	(89)[e]
	81	91/ 9	10.0/**90.0**	(80)
	85	91/ 9	9.0/**91.0**	(82)[e]
	60	91/ 9	7.5/**92.5**	(85)[f]

Catalyst A: Yb(OTf)$_3$+(R)-(+)-binaphthol+cis-1,2,6-trimethylpiperidine+MS4A+3-acetyl-1,3-oxazolidin-2-one (**30**)
Catalyst B: Yb(OTf)$_3$+(R)-(+)-binaphthol+cis-1,2,6-trimethylpiperidine+MS4A+3-phenylacetylacetone (PAA)
[a] 1,2,2,6,6-Pentamethylpiperidine was used instead of 1,2,6-trimethylpiperidine.
[b] Enantiomer ratios of endo adducts.
[c] Without additive.
[d] 2R,3R/2S,3S.
[e] Tm(OTf)$_3$.
[f] Er(OTf)$_3$ was used instead of Yb(OTf)$_3$.

These exciting selectivities are believed to be strongly dependent on the specific coordination number of Yb(III) [69] (Scheme 11). Two binding sites for the ligands are now postulated in the Yb catalysts. **29** or **30** coordinates in site A under equilibrium conditions to stabilize the original catalyst system. When **29** coordinates Yb(III), cyclopentadiene attacks from the si face of **29** (site A favors si face attack). On the other hand, in catalyst B (the original catalyst system and PAA), site A is occupied by PAA [75]. Since another coordination site still remains in the Yb(III) catalyst owing to the specific coordination numbers, **29** coordinates at site B and cyclopentadiene attacks from the re face (site B favors re face attack).
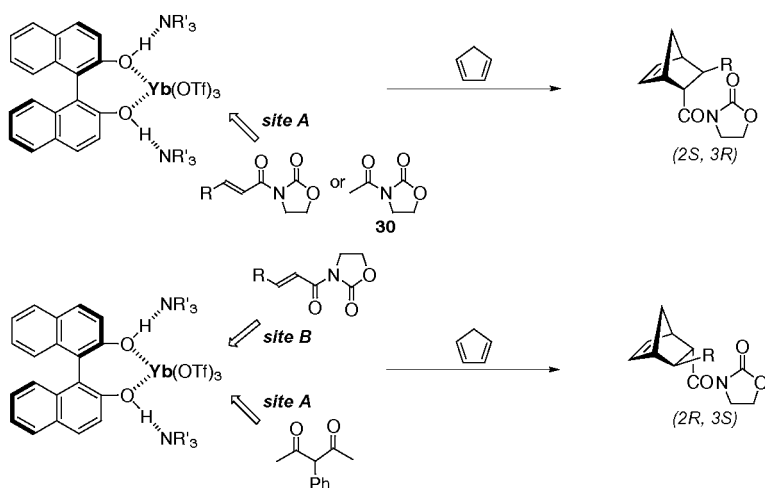
Scheme 11

Table 27. Effect of Ln(OTf)$_3$

Ln	Yield/%	endo/exo	2S,3R/2R,3S (ee(%))[a]	
			Catalyst A	
Lu	60	89/11	96.5/3.5	(93)
Yb	77	89/11	96.5/3.5	(93)
Tm	46	86/14	87.5/12.5	(75)
Er	24	83/17	84.5/15.5	(69)
Ho	12	73/27	62.5/37.5	(25)
Y	6	70/30	60.0/40.0	(20)
Gd	0	—	—	—

Ln	Yield/%	endo/exo	2S,3R/2R,3S (ee (%))[a]	
			Catalyst B	
Lu	30	89/11	24.5/75.5	(51)
Yb	88	92/8	15.0/85.0	(70)
Tm	72	91/9	13.0/87.0	(74)
Er	59	90/10	13.0/87.0	(74)
Ho	70	84/16	21.0/79.0	(58)
Y	85	91/9	19.5/80.5	(61)
Gd	61	85/15	28.5/71.5	(43)

[a] Enantiomer ratios of *endo* adducts.

The effect of other lanthanide triflates was also examined. As shown in Table 27, lanthanide elements strongly influenced the yields and selectivities. A slight difference between the two catalyst systems (catalysts A and B) on the ef-
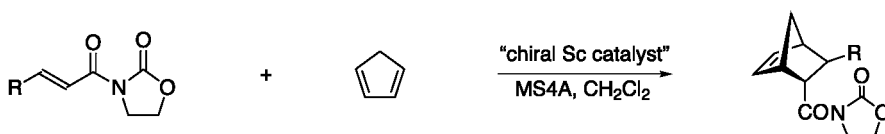
Table 28. Enantioselective Diels-Alder reactions using a chiral scandium catalyst

Dienophile	Catalyst/mol%	Yield/%	*endo/exo*	ee/% (*endo*)
	20	94	89/11	92 (2*S*,3*R*)
	10	84	86/14	96 (2*S*,3*R*)
	5	84	87/13	93 (2*S*,3*R*)
	3	83	87/13	92 (2*S*,3*R*)
	20	99	89/11	93 (2*R*,3*R*)
Ph	10	96	90/10	97 (2*R*,3*R*)
	20	95	78/22	74 (2*S*,3*R*)
n-Pr	10	86	78/22	75 (2*S*,3*R*)

fect of the lanthanide elements was also observed. In catalyst A, lutetium triflate $(Lu(OTf)_3)$ was also effective in generating the *endo* Diels-Alder adduct in 93% ee. The yields and selectivities diminished rapidly in accordance with the enlargement of the ionic radii. In catalyst B, on the other hand, the best results were obtained when thulium triflate $(Tm(OTf)_3)$ or erbium triflate $(Er(OTf)_3)$ was employed. Deviations to either larger or smaller ionic radii resulted in decreased selectivities, although the Diels-Alder adduct was obtained in an 85% yield with good selectivities (*endo/exo*=92/8, *endo* isomer=61% ee) even when holmium triflate $(Ho(OTf)_3)$ was used.

Although $Sc(OTf)_3$ has slightly different properties compared with other lanthanide triflates, the chiral Sc catalyst could be prepared from $Sc(OTf)_3$, (*R*)-(+)-binaphthol, and a tertiary amine in dichloromethane [76]. The catalyst was also found to be effective in the Diels-Alder reactions of acyl-1,3-oxazolidin-2-ones with dienes. The amines employed in the preparation of the catalyst influenced the enantioselectivities strongly. For example, in the Diels-Alder reaction of 3-(2-butenoyl)-1,3-oxazolidin-2-one with cyclopentadiene $(CH_2Cl_2, 0 °C)$, the enantiomeric excesses of the *endo* adduct depended crucially on the amines employed; aniline, 14% ee; lutidine, 46% ee; triethylamine, 51% ee; 2,2,6,6-tetramethylpiperidine, 51% ee; diisopropylethylamine, 69% ee; 2,6-dimethylpiperidine, 69% ee; 1,2,2,6,6-pentamethylpiperidine, 72% ee; and *cis*-1,2,6-trimethylpiperidine, 84% ee.

Several examples of the chiral Sc(III)-catalyzed Diels-Alder reactions are shown in Table 28. The highest enantioselectivities were observed when *cis*-1,2,6-trimethylpiperidine was employed as an amine. 3-(2-Butenoyl)-, 3-cinnamoyl-, and 3-(2-hexenoyl)-1,3-oxazolidin-2-ones reacted with cyclopentadi-
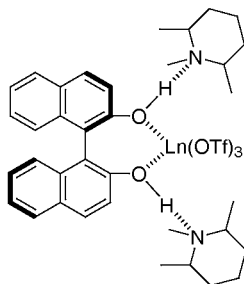
Scheme 12

ene smoothly in the presence of the chiral Sc catalyst to afford the corresponding
Diels-Alder adducts in high yields and high selectivities. It should be noted that
even 3 mol% of the catalyst was enough to complete the reaction and the *endo*
adduct was obtained in a 92% ee.

The catalyst was also found to be effective for the Diels-Alder reactions of an
acrylic acid derivative [77]. 3-Acryloyl-1,3-oxazolidin-2-one reacted with 2,3-
dimethylbutadiene to afford the corresponding Diels-Alder adduct in a 78%
yield and a 73% ee, whereas the reaction of 3-acryloyl-1,3-oxazolidin-2-one with
cyclohexadiene gave a 72% ee for the *endo* adduct (88% yield, *endo/exo*=100/0).

Similar to the chiral Yb catalyst, aging was observed in the chiral Sc catalyst.
It was also found that **30** or 3-benzoyl-1,3-oxazolidin-2-one was a good additive
for stabilization of the catalyst, but that reverse enantioselectivities by additives
were not observed. This can be explained by the coordination numbers of
Yb(III) and Sc(III); while Sc(III) has up to seven ligands, specific coordination
numbers of Yb(III) allow up to twelve ligands [69, 78].

As for the chiral ytterbium and scandium catalysts, the following structures
were postulated. The unique structure shown in Scheme 12 was indicated by
^{13}C NMR and IR spectra. The most characteristic point of the catalysts was the
existence of hydrogen bonds between the phenolic hydrogens of (*R*)-(+)-
binaphthol and the nitrogens of the tertiary amines. The ^{13}C NMR spectra indi-
cated these interactions, and the existence of the hydrogen bonds was confirmed
by the IR spectra [79]. The coordination form of these catalysts may be similar
to that of the lanthanide(III)-water or -alcohol complex [78]. It is noted that the
structure is quite different from those of conventional chiral Lewis acids based
on aluminum [80], boron [81], or titanium [82]. In the present chiral catalysts,
the axial chirality of (*R*)-(+)-binaphthol is transferred via the hydrogen bonds
to the amine parts, which shield one side of the dienophile effectively [83]. This
is consistent with the experimental results showing that amines employed in the
preparation of the chiral catalysts strongly influenced the selectivities and that
bulky amines gave better selectivities.

Although the transition states of the chiral lanthanide(III)-catalyzed reac-
tions are rather complicated due to the specific coordination number and stere-
ochemistry of lanthanide(III), the sense of asymmetric induction in the chiral

Scheme 13

Yb Catalyst A: $Yb(OTf)_3$ + (R)-(+)-binaphtol + TMP+30
Yb Catalyst B: $Yb(OTf)_3$ + (R)-(+)-binaphtol + TMP+PAA
Sc Catalyst: $Sc(OTf)_3$ + (R)-(+)-binaphtol + TMP
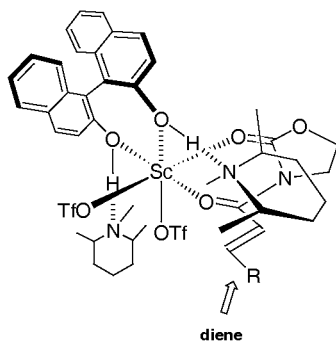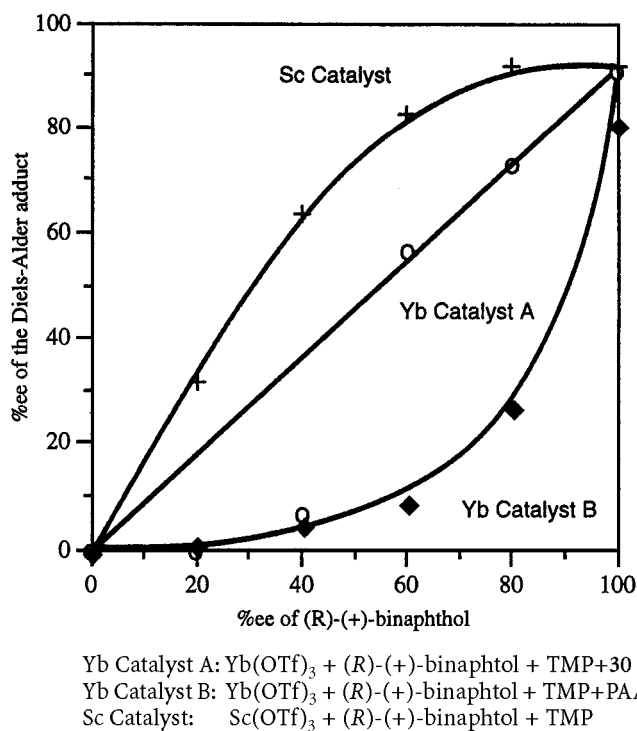
Fig. 1. Correlation between the ee of the Diels-Alder adduct and the ee of (R)-(+)-binaphthol

scandium-catalyzed reactions can be rationalized by assuming an intermediate octahedral Sc(III)-dienophile complex (Scheme 13). The axial chirality of (R)-(+)-binaphthol is transferred to the amine, the *re* face of the acyl-1,3-oxazolidin-

2-one is effectively shielded by the amine part, and a diene approaches the dienophile from the *si* face to afford the adduct in a high enantioselectivity.

It was also suggested that aggregation of the catalysts influenced the selectivities in the Diels-Alder reactions, and the reaction of 3-(2-butenoyl)-1,3-oxazolidin-2-one with cyclopentadiene using (R)-(+)-binaphthol in lower enantiomeric excesses was examined [84]. The results are shown in Fig. 1. Very interestingly, a positive nonlinear effect was observed in the chiral Sc catalyst. In the chiral Yb catalysts, on the other hand, the effect was dependent on the additives. The extent of asymmetric induction in catalyst A did not deviate from the enantiomeric excesses of (R)-(+)-binaphthol in the range 60–100% ee [85], while a negative nonlinear effect was observed in catalyst B. These results can be ascribed to a difference in aggregation between the Sc catalyst, Yb catalyst A, and Yb catalyst B.

8
Asymmetric Aza Diels-Alder Reactions

While asymmetric reactions using chiral Lewis acids have been demonstrated to achieve several highly enantioselective carbon-carbon bond-forming processes using catalytic amounts of chiral sources [86], chiral Lewis acid-catalyzed asymmetric reactions of nitrogen-containing substrates are rare, probably because most chiral Lewis acids would be trapped by the basic nitrogen atoms to block the catalytic cycle. For example, aza Diels-Alder reactions are one of the most basic and versatile reactions for the synthesis of nitrogen-containing heterocyclic compounds [58, 87]. Although asymmetric versions using chiral auxiliaries or a stoichiometric amount of a chiral Lewis acid have been reported [88], examples using a catalytic amount of a chiral source are unprecedented.

In the previous section, lanthanide triflates were shown to be excellent catalysts for achiral aza Diels-Alder reactions. While stoichiometric amounts of Lewis acids are required in many cases, a small amount of the triflate effectively catalyzes the reactions. On the other hand, chiral lanthanide Lewis acids have been developed to realize highly enantioselective Diels-Alder reactions of 2-oxazolidin-1-one with dienes [89]. The reaction of *N*-benzylideneaniline with cyclopentadiene was first performed under the influence of 20 mol% of a chiral ytterbium Lewis acid prepared from ytterbium triflate (Yb(OTf)$_3$), (R)-(+)-1,1'-bi-naphthol (BINOL), and trimethylpiperidine (TMP). The reaction proceeded smoothly at room temperature to afford the desired tetrahydroquinoline derivative in a 53% yield, although no chiral induction was observed. At this stage, it was indicated that bidentate coordination between a substrate and a chiral Lewis acid would be necessary for reasonable chiral induction. *N*-Benzylidene-2-hydroxyaniline (**31a**) was then prepared, and the reaction with cyclopentadiene (**32a**) was examined. It was found that the reaction proceeded smoothly to afford the corresponding 8-hydroxyquinoline derivative (**33a**) [90] in a high yield. The enantiomeric excess of the *cis* adduct in the first trial was only 6%; however, the selectivity increased when diazabicyclo-[5,4,0]-undec-7-ene (DBU) was used in-
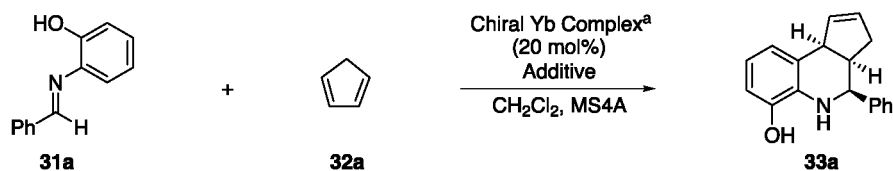
Table 29. Effect of additive

Additive[b]/mol%	Temp/°C	Yield/%	cis/trans	ee/% (cis)
—	0	71	98 / 2	62
—	-15 to 0	48	99 / 1	68
MID (20)	-15 to 0	21	98 / 2	91
DTBP (20)	0	49	95 / 5	31
DTBP (100)	0	67	99 / 1	61
DMP (100)	0	14	98 / 2	56
DTBMP (100)	-15	82	>99 / 1	70
DTBP (100)	-15	92	>99 / 1	71

[a] Prepared from $Yb(OTf)_3$, (R)-$(+)$-BINOL, and DBU.
[b] MID: 1-Methylimidazole. DTBP: 2,6-di-t-butylpyridine. DMP: 2,6-dimethylpyridine. DT-BMP: 2,6-di-t-butyl-4-methylpyridine.

stead of TMP (Table 29). It was also indicated that the phenolic hydrogen of **31a** would interact with DBU, which should interact with the hydrogen of (R)-$(+)$-BINOL [91], to decrease the selectivity. Additives which interact with the phenolic hydrogen of **31a** were then examined. When 20 mol% of N-methylimidazole (MID) was used, 91% ee of the *cis* adduct was obtained; however, the chemical yield was low. Other additives were screened and it was found that the desired tetrahydroquinoline derivative was obtained in a 92% yield with high selectivities (*cis/trans*>99/1, 71% ee), when 2,6-di-t-butyl-4-methylpyridine (DT-BMP) was used.

Other substrates were tested, and the results are summarized in Table 30 [92]. Vinyl ethers (**32b–32d**) also worked well to afford the corresponding tetrahydroquinoline derivatives (**33b–33e**) in good to high yields with good to excellent diastereo- and enantioselectivities (entries 1–9). Use of 10 mol% of the chiral catalyst also gave the adduct in high yields and selectivities (entries 2, 6). As for additives, 2,6-di-t-butylpyridine (DTBP) gave the best result in the reaction of imine **31a** with ethyl vinyl ether (**32b**), while higher selectivities were obtained when DTBMP or 2,6-diphenylpyridine (DPP) was used in the reaction of imine **31a** with **32b**. This could be explained by the slight difference in the asymmetric environment created by $Yb(OTf)_3$, (R)-$(+)$-BINOL, DBU, and the additive (see below). While use of butyl vinyl ether (**32c**) decreased the selectivities (entry 7), dihydrofurane (**32d**) reacted smoothly to achieve high levels of selectivity (entries 8, 9). It was found that the imine (**31c**) prepared from cyclohexanecar-
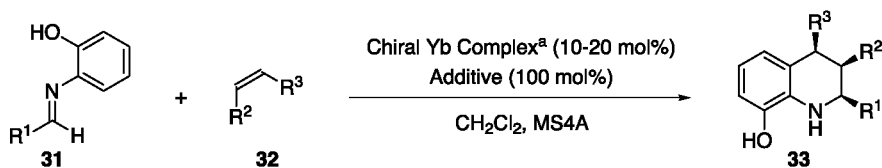
Table 30. Asymmetric synthesis of tetrahydroquinoline derivatives

Entry	R[1]		Alkene		Additive[a]	Amount of Catalyst /mol%	Temp /°C	Product	Yield /%	cis/trans	Ee/% (cis)
1	Ph	(31a)	OEt	(32b)	DTBP	20	-45	33b	58	94 / 6	61
2	Ph	(31a)		32b	DTBP	10	-45	33b	52	94 / 6	77
3	α-Naph	(31b)		32b	DTBP	20	-15	33c	69	>99 / 1	86
4	α-Naph	(31b)		32b	DPP[b]	20	-15	33c	65	99 / 1	91
5	α-Naph	(31b)		32b	DTBMP	20	-15	33c	74	>99 / 1	91
6	α-Naph	(31b)		32b	DTBMP	10	-15	33c	62	98 / 2	82
7	α-Naph	(31b)	OBu	(32c)	DTBMP	20	-15	33d	80	66 / 34	70
8	α-Naph	(31b)	(furan)	(32d)	DTBMP	20	-15	33e	90	91 / 9	78
9	α-Naph	(31b)		32d	DPP[b]	20	-15	33e	67	93 / 7	86
10	α-Naph	(31b)	(cyclopentadiene)	(32a)	DTBMP	20	-15	33f	69	>99 / 1	68
11[c]	c-C$_6$H$_{11}$	(31c)		32a	DTBMP	20	-15	33g	58	>99 / 1	73

[a] See Table 29.
[b] 2,6-Diphenylpyridine.
[c] Sc(OTf)$_3$ was used.
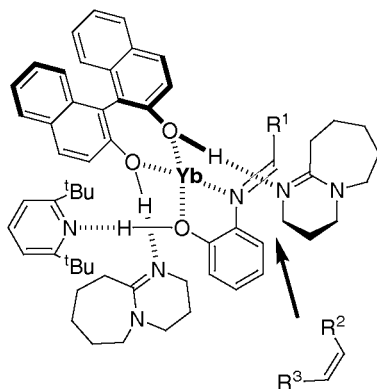
Scheme 14

boxaldehyde and 2-hydroxyaniline was unstable and difficult to purify. The asymmetric aza Diels-Alder reaction was successfully carried out using the three component coupling procedure (successively adding the aldehyde, the amine, and cyclopentadiene) in the presence of $Sc(OTf)_3$ (instead of $Yb(OTf)_3$), (*R*)-(+)-BINOL, DBU, and DTBMP.

Assumed transition state of this reaction is shown in Scheme 14. $Yb(OTf)_3$, (*R*)-(+)-BINOL, and DBU form a complex with two hydrogen bonds, and the axial chirality of (*R*)-(+)-BINOL is transferred via the hydrogen bonds to the amine parts. The additive would interact with the phenolic hydrogen of the imine, which is fixed by bidentate coordination to Yb(III). Since the top face of the imine is shielded by the amine, the dienophiles approach from the bottom face to achieve high levels of selectivity.

Thus, catalytic asymmetric aza Diels-Alder reactions of imines with alkenes have been developed using a chiral lanthanide Lewis acid, to afford 8-hydroxyquinoline derivatives in high yields with high diastereo- and enantioselectivities. Characteristic points of this reaction are as follows.

i.   Asymmetric aza Diels-Alder reactions between achiral azadienes and dienophiles have been achieved using a catalytic amount of a chiral source.

ii. The unique reaction pathway in which the chiral Lewis acid activates not dienophiles but dienes, is revealed. In most asymmetric Diels-Alder reactions reported using chiral Lewis acids, the Lewis acids activate dienophiles [86, 93].

iii. A unique lanthanide complex including an azadiene and an additive, which is quite different from the conventional chiral Lewis acids, has been developed.

9
Catalytic Enantioselective 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions between nitrones and alkenes are most useful and convenient for the preparation of isoxazolidine derivatives, which are readily converted to 1,3-amino alcohol equivalents under mild reducing conditions [94]. In spite of the importance of chiral amino alcohol units for the synthesis of biologically important alkaloids, amino acids, b-lactams, and amino sugars, etc. [95], catalytic enantioselective 1,3-dipolar cycloadditions remain relatively unexplored [95, 96]. Catalytic enantioselective 1,3-dipolar cycloadditions of nitrones with alkenes using a chiral lanthanide catalyst were investigated [97, 98]. First, the 1,3-dipolar cycloaddition reaction of *N*-benzylidenebenzylamine *N*-oxide with 3-(2-butenoyl)-1,3-oxazolidin-2-one was performed in the presence of a chiral Yb(III) catalyst (20 mol%) prepared from $Yb(OTf)_3$, (*S*)-1,1'-binaphthol ((*S*)-BINOL), and triethylamine (Et_3N). The reaction proceeded smoothly at room temperature to afford the corresponding isoxazolidine derivative in a 65% yield with high *endo/exo* selectivity (99/1), and a moderate ee of the *endo* adduct was observed (Table 31). The enantiomeric excess was improved to 78% when *cis*-1,2,6-trimethylpiperidine (TMP) was used instead of Et_3N. Further-
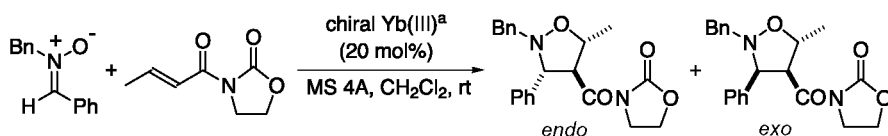
Table 31. Effect of amines

Amine	Yield/%	*endo /exo*	ee/%[b]
Et$_3$N	65	99/1	63
*i*Pr$_2$NEt	73	>99/1	62
cis -1,2,6-TMP[c]	73	99/1	78
(*R*)-MPEA [d]	92	>99/1	71
(*S*)-MPEA	80	97/3	35
(*R*)-MNEA [e]	92	99/1	96
(*S*)-MNEA	87	99/1	62

[a] Chiral Yb(III)=Yb(OTf)$_3$+(*S*)-BINOL+amine.
[b] Ee of the *endo* adducts.
[c] *cis*-1,2,6-Trimethylpiperidine.
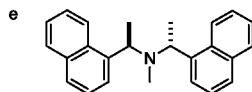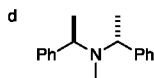
more, it was found that *use of chiral amines influenced the selectivity dramatically, and combination of the chirality of BINOL and the amine was crucial for the selectivity.* Namely, 71% ee of the *endo* adduct was obtained in the model reaction using a catalyst prepared by the combination of (*S*)-BINOL and *N*-methyl-bis[(*R*)-1-phenylethyl]amine ((*R*)-MPEA), while only 35% ee was observed by the combination of (*S*)-BINOL and (*S*)-MPEA. Moreover, it was found that 96% ee of the *endo* adduct was obtained with an excellent yield (92%) and diastereo-selectivity (*endo/exo*=99/1) by the combination of (*S*)-BINOL and a newly-prepared chiral amine, *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine ((*R*)-MNEA) [99]. The chiral Yb(III) catalyst thus prepared has two independent chiralities (hetero-chiral Yb(III) catalyst, see below) and it was found that the sense of the chiral induction in these reactions was mainly determined by BINOL and that the chiral amine increased or decreased the induction relatively.

Several examples of the 1,3-dipolar cycloadditions between nitrones and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones using the novel hetero-chiral Yb(III) catalyst are shown in Table 32. In most cases, the desired isoxazolidine derivatives were obtained in excellent yields with excellent diastereo- and enantioselectivities. It is noted that high levels of selectivities were attained at room temperature. Nitrones derived from aromatic and heterocyclic aldehydes gave satisfactory re-
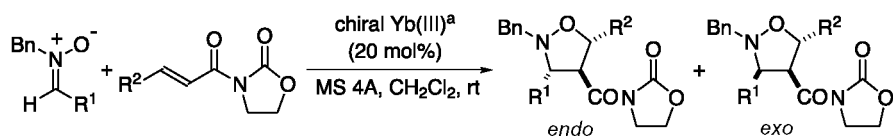
Table 32. Catalytic enantioselective 1,3-dipolar cycloadditions

R^1	R^2	Yield/%	endo/exo	ee/%[b]
Ph	CH_3	92	99/1	96
p-Cl-Ph	CH_3	93	99/1	92
p-MeO-Ph	CH_3	82	95/5	90
2-furyl	CH_3	89	95/5	89
1-naphthyl	CH_3	88	98/2	85
Ph	H	91	>99/1	79
Ph	C_3H_7	89	98/2	93
C_2H_5	CH_3	88	53/47	96

[a] Chiral Yb(III)=Yb(OTf)$_3$+(S)-BINOL+(R)-MNEA.
[b] Ee of the endo adducts.
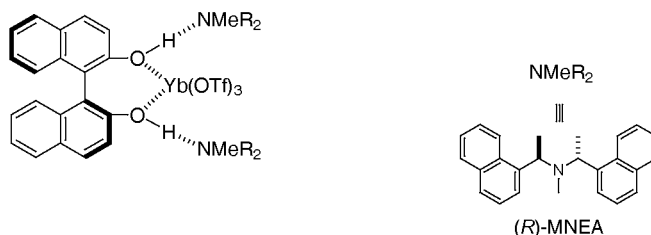
Scheme 15

sults, and even in the reaction using the nitrone derived from an aliphatic alde-hyde, the cycloaddition proceeded smoothly to give the endo adduct in an excel-lent enantiomeric excess, albeit low endo/exo selectivity was observed. Moreo-ver, it was found that alkenes which could be employed in the present 1,3-dipolar cycloaddition were not limited to 3-(2-alkenoyl)-1,3-oxazolidin-2-one deriva-tives. When N-phenylmaleimide was used as a dipolarophile, the desired isoxa-zolidine derivative was obtained in a 70% yield with endo/exo>99/1, and the enantiomeric excess of the endo adduct was 70% ee under the standard reaction conditions [100, 101].

As for the structure of the hetero-chiral Yb(III) catalyst, the following struc-ture was supported (Scheme 15). Actually, the existence of hydrogen bonds be-tween the phenolic hydrogens of (S)-BINOL and the nitrogens of (R)-MNEA was confirmed by the IR spectra of the catalyst [79, 102].
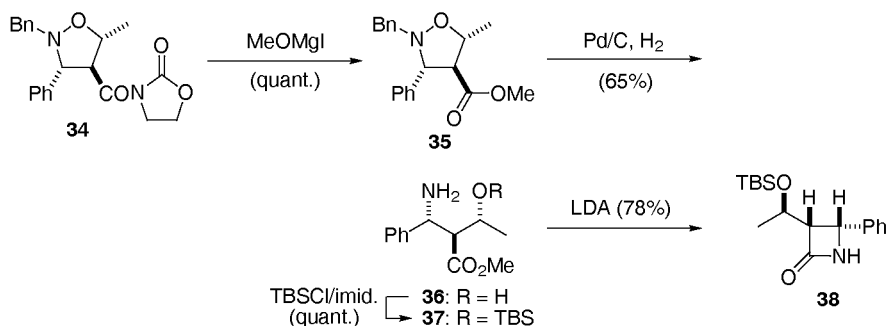
Scheme 16

3-Hydroxyethyl-b-lactam derivative was synthesized using the present reactions (Scheme 16). Isoxazolidine derivative **34**, prepared via the catalytic enantioselective 1,3-dipolar cycloaddition, was treated with methoxymagnesium iodide [103] to give methyl ester **35**. Reductive N-O bond cleavage and deprotection of the *N*-benzyl part of **35** was performed in the same pot using Pd/C under hydrogen atmosphere (10 kg/cm^2) [104] to afford amino ester **36**. After the resulting alcohol moiety was protected as its *t*-butyldimethylsilyl (TBS) ether, cyclization of **37** proceeded smoothly using lithiumdiisopropylamide (LDA) [105] to afford the corresponding b-lactam (**38**) [106] in a good yield.

10
Conclusions

Lanthanide triflates are new types of Lewis acids different from typical Lewis acids such as AlCl$_3$, BF$_3$, SnCl$_4$, etc. While most Lewis acids are decomposed or deactivated in the presence of water, lanthanide triflates are stable and works as Lewis acids in water solutions. Many nitrogen-containing compounds such as imines and hydrazones are also successfully activated by using a small amount of Ln(OTf)$_3$. Lanthanide triflates are also excellent Lewis acid catalysts in organic solvents. A catalytic amount of Ln(OTf)$_3$ is enough to complete reactions in most cases. In addition, Ln(OTf)$_3$ can be recovered after reactions are completed and can be reused.

Recently, polymer-supported lanthanide catalysts have beem of great interest, and these topics are discussed elsewhere. Use of lanthanide catalysts in solid-phase organic synthesis is now well-recognized [107]. There have also been many transformations other than carbon-carbon bond-forming reactions in organic synthesis using lanthanide triflates as catalysts, and all these will be reviewed in the near future.

11
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89. Kobayashi S, Ishitani H, Hachiya I, Araki M (1994) Tetrahedron 50:11,623
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94. (a) Tufariello JJ (1984) In: Padwa A (ed) 1,3-Dipolar cycloaddition chemistry, vol 2. Wiley, Chichester, p 83; (b) Torssell KBG (1988) Nitrile oxides, nitrones and nitronates in organic synthesis. VCH, Weinheim
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97. It was recently found that lanthanide triflates are excellent catalysts in achiral 1,3-dipolar cycloadditions between nitrones and alkenes and also in three-component coupling reactions of aldehydes, hydroxylamines, and alkenes: Kobayashi S, Akiyama R,

Kawamura M, Ishitani H (1997) Chem Lett 1039. Cf. Minakata S, Ezoe T, Ilhyong R, Komatsu M, Ohshiro Y (1997) The 72nd Annual Meeting of the Chemical Society of Japan, Tokyo, 2F3 37. See also [98]

98. Quite recently, Jøgensen et al. reported similar asymmetric 1,3-dipolar cycloadditions using Yb(OTf)$_3$-PyBOX; however, enantiomeric excesses obtained were up to 73%: Sanchez-Blanco AI, Gothelf KV, Jøgensen KA (1997) Tetrahedron Lett 38:7923

99. (*R*)-MNEA was prepared from (*R*)-1-(1-naphthyl)ethylamine

100. It is believed that bidentate coordination (ex. Yb(III)-3-(2-alkenoyl)-1,3-oxazolidin-2-one) is necessary to obtain high selectivities in many chiral lanthanide-catalyzed reactions [101]. These results are very interesting and promising because it has been shown that even monodentate coordination can achieve good selectivities by using the hetero-chiral Yb(III) catalyst

101. [72, 73, 76, 89, 91]. See also (a) Marko IE, Evans GR (1994) Tetrahedron Lett 35:2771; (b) Burgess K, Lim H-J, Porte AM, Sulikowski GA (1996) Angew Chem, Int Ed Engl 35:220

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Lanthanide- and Group 3 Metallocene Catalysis in Small Molecule Synthesis

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Although the polymerization prowess of organolanthanide complexes has been known for some time, efforts to apply these catalysts to small molecule synthesis have only recently begun. The selectivity of these metallocenes is predominantly steric in nature, and they are compatible with a wide variety of organic functional groups. A review of their use in olefin hydrogenation, hydrosilylation, and polyene cyclization with emphasis on chemoselectivity and diastereoselectivity is presented here. The various ways in which the catalysts and reagents can be tuned to produce the desired products is also discussed.

Keywords: Metallocenes, Catalysis, Cyclization, Hydrogenation, Silylation

1
Introduction

Carbon-carbon bond-forming reactions constitute the heart and soul of synthetic organic chemistry. Nowhere are these reactions more prolific than in commercial polymerization reactions, where worldwide production of polyethylene and polypropylene is carried out on enormous scale. The polymerization of α-olefins employing Ziegler-Natta catalysts [1], organolanthanides and group 3 organometallics [2], palladium and nickel cationic complexes [3], and related catalysts [4] have revolutionized the controlled synthesis of polymers derived from terminal alkenes. Group 3 organometallics and organolanthanides in particular are among the most active known catalysts in olefin polymerization chemistry [5]. However, in spite of the spectacular ability of these complexes to generate new carbon-carbon bonds in polymerization reactions, relatively little effort has been made in applying these catalytic systems to small molecule synthesis through cyclization reactions of dienes, enynes, and related substrates

$$\text{(1)}$$
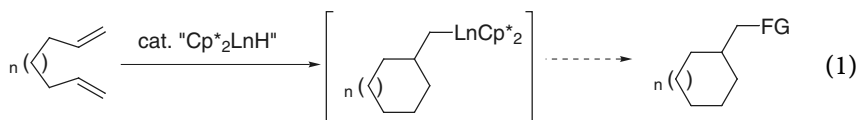
To be sure, the extrapolation of reactivity from ethylene and propylene to highly functionalized organic molecules is daunting, and many questions arise concerning the suitability of the aforementioned catalysts within this context. For example, only recently have available catalysts been able to polymerize anything but monosubstituted alkenes. Even allylic substitution of such alkenes has presented difficulties for the sterically sensitive organometallic complexes [6]. To be broadly applicable, catalysts would have to be developed that would allow insertion of more highly substituted alkenes. Functional group compatibility was also of concern. Most polar functional groups (even ethers) were reported to either react with the organometallics [7] or irreversibly bind so as to inhibit catalysis [8]. Again, to be considered as part of a general synthetic method it was imperative that organometallic catalysts be developed that could tolerate a wide range of common organic functionality. Many of the complexes, particularly the organolanthanides and group 3 organometallics, are extraordinarily air-sensitive and require glove-box or Schlenk-line techniques for their handling. The synthesis of reasonably air-stable complexes would facilitate the introduction of these catalysts to a broader range of applications. Finally, several issues of selectivity would have to be addressed. First, chemoselectivity in the insertion of a single alkene or alkyne in a polyunsaturated system would be required. A high degree of regioselectivity in this insertion is also essential. Diastereoselectivity in reactions of chiral substrates and prochiral unsaturated systems would necessitate examination. Finally, chiral, nonracemic complexes would have to be developed in order to meet the challenges of modern synthetic organic chemistry.

This contribution is not intended to be a comprehensive review of the application of group 3 metal and lanthanide metallocenes to selective organic synthesis, but rather seeks to highlight some of the general characteristics of these catalysts and to provide a critical discussion of the reactions to which they have been applied. Emphasis has been placed upon the means by which some of the potential problems delineated above have been addressed and upon the application of these catalytic species to novel methods in synthetic organic chemistry.

2
## General Features of the Catalytic Systems and the Olefin Insertion Reaction

The key step in nearly all of the catalytic processes to be discussed is olefin insertion into a metal hydride [Eq. (2)] or organometallic species [Eq. (3)]. These hydrometallation and carbometallation processes also form the basis for the polymerization of alkenes. Olefin insertions generally occur with the same regioselectivity as hydroboration reactions [9], with the bulky metal and associated ligands residing at the least hindered site of the two carbon reactive unit.

$$\text{"Cp*}_2\text{LnH"} \quad + \quad \text{CH}_2\text{=CHR} \quad \longrightarrow \quad \text{Cp*}_2\text{LnCH}_2\text{CH}_2\text{R} \tag{2}$$

$$\text{Cp*}_2\text{LnR} \quad + \quad \text{CH}_2\text{=CHR'} \quad \longrightarrow \quad \text{Cp*}_2\text{LnCH}_2\text{CHRR'} \tag{3}$$
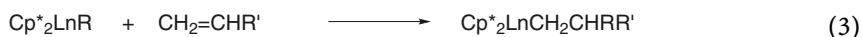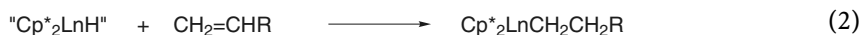
In most instances these reactions are extremely exothermic and effectively irreversible under reasonable reaction conditions [10]. Even *tert*-butyl-substituted organolanthanides (prepared by other methods) exhibit significant kinetic stability [11].

The organolanthanide- and group 3 organometallic catalysts are highly electrophilic species. Although there is a significant electronic driving force in the olefin insertion process, for the most part steric factors predominate. Much of this can be attributed to the effects of coordinative unsaturation at the metal center. High reactivity is associated with free coordination sites and terminal (non-bridging) ligands [12]. The requirement for free coordination sites dictates that noncoordinating solvents be utilized for the catalytic reactions. Thus common ether solvents lead to low catalytic turnover rates [10] and can even deactivate catalysts via ether cleavage reactions [7, 13]. Consequently, hydrocarbon solvents are used exclusively in the catalytic reactions.

Although it would seem logical to utilize the most sterically unhindered ligands about the metal to achieve maximum reactivity with hindered alkenes, in fact there is a delicate balance that must be achieved between the "openness" of the metal center and the tendency for the organometallic hydrides to undergo a deactivating ligand redistribution [14] or to dimerize, forming hydride-bridged dimers [Eq. (4)] [10].

$$2 \text{ Cp}_2\text{LnH} \quad \rightleftharpoons \quad \text{Cp}_2\text{Ln} \overset{\text{H}}{\underset{\text{H}}{<}} \text{LnCp}_2 \tag{4}$$
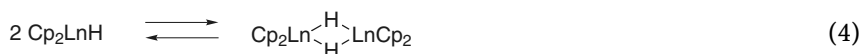
These dimers are less reactive or unreactive in catalytic reactions of interest, and thus some substitution on the cyclopentadienyl ligands is necessary to prevent dimer formation through steric hindrance to association. Pentamethylcyclopentadienyl (Cp*) ligands are useful for this, and lead to catalytic systems that are highly reactive and yet exquisitely selective in the insertion of monosubstituted alkenes. One such precatalyst system is the yttrium complex Cp*$_2$YMe•THF. Although Lewis bases normally depress catalytic activity because they compete for empty coordination sites on the catalyst, in this precatalyst the single THF of solvation appears to catalyze the hydrometallation process [Eq. (5)] [15] in the same manner that Lewis bases catalyze the hydroboration of olefins with 9-BBN [16]:

$$\text{Cp*}_2\text{Y}\underset{\text{H}}{\overset{\text{H}}{<}}\text{YCp*}_2 \quad + \quad 2 \text{ THF} \quad\longrightarrow\quad 2 \text{ Cp*}_2\text{YH•THF} \tag{5}$$
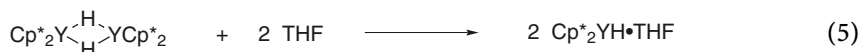
A related complex lacking a THF of association, Cp*$_2$YCH(TMS)$_2$, is orders of magnitude less reactive than Cp*$_2$YMe•THF in reactions with monosubstituted alkenes. Addition of one molar equivalent of THF per equivalent of Cp*$_2$YCH(TMS)$_2$ restores catalytic activity to the level of the methyl complex [17]. Apparently, this THF also depresses the rate of σ-bond metathesis (see below) relative to olefin insertion [10], with important ramifications for cyclization/termination processes to be discussed later. Curiously, this THF effect appears unique to the Cp*$_2$YR system.

Unfortunately, the yttrium hydride complex Cp*$_2$YH is very hindered about the reactive metal center and does not react readily with 1,1-disubstituted alkenes and more highly hindered olefins. Three general catalyst modifications have been utilized to overcome this difficulty. The first is the incorporation of lanthanide metals with larger ionic radii. Because of the lanthanide contraction, early lanthanides have a larger ionic radius than the late lanthanides. Placement of one of the larger metal ions into the ligand system has the effect of opening it up, allowing access to more hindered alkenes. This strategy has its limits, and to create even more accessible metal centers the ligand system itself must be changed. Incorporation of a single bulky substituent onto the cyclopentadienyl units has been utilized to open the reactive metal center. Substituents such as *tert*-butyl groups and trimethylsilyl groups appear to prevent extensive hydride dimer formation, but at the same time leave the metal center relatively open for interaction with olefins. An example of such a precatalyst is displayed in Fig. 1. Although the methyl precatalyst is a dimer, the active hydride catalyst is most likely a monomer, and is capable of rapid olefin insertion of most 1,1-disubstituted alkenes [18]. Another interesting feature of the catalyst is its unusual stability. Members of this class of precatalysts have been weighed in the air and utilized in hydrosilylation reactions performed with normal procedures for the benchtop handling of air-sensitive materials [9, 19].

The third strategy that has been utilized to provide more open access to the metal is to utilize "hinged" cyclopentadienyl ligands. A one atom bridge between two cyclopentadienyl units serves to increase the angle between them, and again
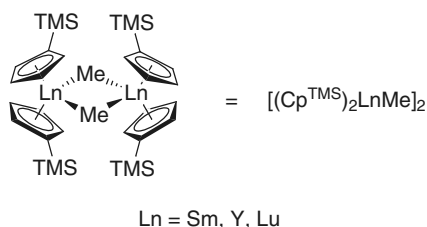
Ln = Sm, Y, Lu

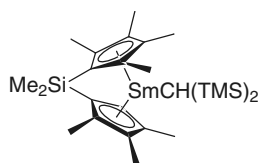**Fig. 1.** Unhindered catalyst systems for reaction with hindered alkenes

Fig. 2. Hinged catalyst system for reaction with hindered alkenes

provides more facile approach of substrate to the metal. Figure 2 depicts one such precatalyst [20].

With a wide range of metals and ligands available [2a, 21], organolanthanide and group 3 organometallic catalysts are readily "tuned" to provide the desired reactivity and selectivity patterns in reactions of interest.

3
Catalytic Hydrogenation Reactions

Organolanthanides and group 3 organometallics are extraordinarily reactive hydrogenation catalysts [22]. They are also relatively challenging to prepare and handle. This, combined with their lack of tolerance to reactive functional groups, makes them less attractive than many transition metal-based catalysts in standard hydrogenation reactions. It is instructive, however, to examine the catalytic cycle of hydrogenation reactions because it serves as a useful model for the other catalytic reactions to be discussed subsequently. Additionally, useful information concerning selectivity has been derived from studies of the hydrogenation reaction.

Transition metal-based hydrogenation reactions most often operate on a catalytic cycle that involves oxidative addition, olefin insertion, and reductive elimination. The mechanistic basis for organolanthanide hydrogenation is quite different, and involves olefin insertion and σ-bond metathesis (Fig. 3).

A σ-bond metathesis initiates the process, converting an organometallic precatalyst into the catalytic hydride species through a four-centered exchange of
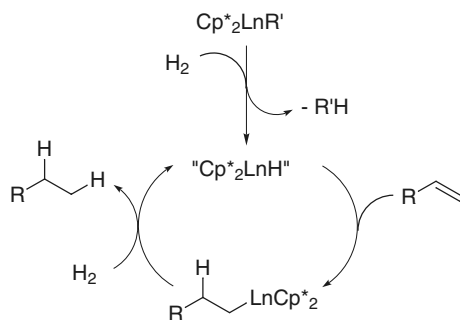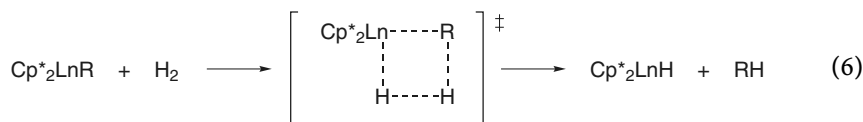
Fig. 3. Catalytic cycle for hydrogenation

ligands [Eq. (6)] [23]. Olefin insertion is the product-determining step of the process, and is generally irreversible under optimal conditions for hydrogenation [10]. A σ-bond metathesis reaction constitutes the final step of the process, wherein the organometallic reacts with hydrogen to release the hydrocarbon and regenerate the active catalyst.

$$Cp^*_2LnR \; + \; H_2 \; \longrightarrow \; \left[\begin{array}{c} Cp^*_2Ln\text{-----}R \\ \vdots \qquad \vdots \\ H\text{-----}H \end{array} \right]^{\ddagger} \; \longrightarrow \; Cp^*_2LnH \; + \; RH \qquad (6)$$

Detailed kinetic studies for organolanthanide-catalyzed hydrogenations have been performed [22]. Although there are some exceptions, for reactive olefins the rate of the reaction is proportional to the product of the catalyst concentration and hydrogen concentration, indicating a rapid olefin insertion and rate limiting σ-bond metathesis. With the exception of cyclohexene, the relative rate constants for hydrogenation of monosubstituted alkenes and a variety of 1,2-disubstituted alkenes are remarkably similar. Nevertheless, synthetically useful selectivities can be achieved with a highly discriminating catalyst (Eqs. 7–9) [24]. For most diene substrates wherein the two alkenes exhibit different reactivities, hydrogen uptake need not be monitored. Even with a highly reactive, strained alkene such as is found in the bicyclo[2.2.1] system, the monosubstituted alkene is so much more reactive that a single equivalent of hydrogen is utilized even in the presence of a vast excess of hydrogen (Eq. 7). Perhaps even more impressive is the selectivity displayed in Eq. (8), wherein substitution at one allylic position of a diene system is sufficient to permit virtually complete selectivity. Most common alcohol protecting groups are tolerated (Eq. 9), but allylic acetate and allylic halide functionalities inhibit catalytic turnover.

$$(7)$$

$$(8)$$

$$(9)$$
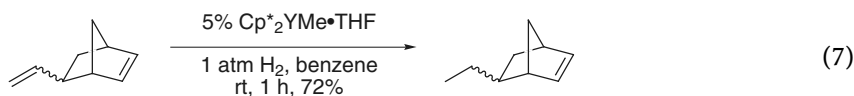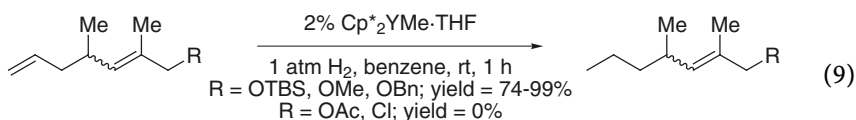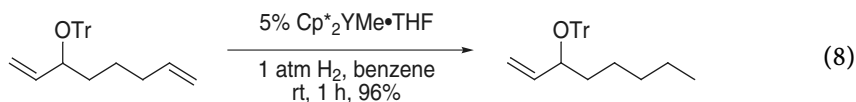
More hindered, less reactive alkenes such as 1,1-disubstituted alkenes require a more open catalyst [25]. For the hydrogenation reaction, the simple alternative of utilizing a samarium- or ytterbium-based catalyst permits these substrates to react effectively, often with high diastereoselectivities (Eqs. 10–12). A variety of alkyl and aryl substituents are tolerated, including a tertiary amine (Eq. 11). Allylic ether substitution, however, inhibits the reaction, even under more vigorous conditions. After initial insertion of the olefin, the Lewis acidic metal center can form a stable five-membered ring chelate with the oxygen, preventing further reaction. In general, the diastereoselectivity of the olefin insertion diminishes when the existing stereogenic center occupies a position that causes less interaction with the bulky organometallic reagent (Eq. 12). The stereochemistry of the products is that predicted by the approach of the bulky organometallic to the less hindered face of the exo-methylene unit.

$$(10)$$

$$(11)$$

$$(12)$$
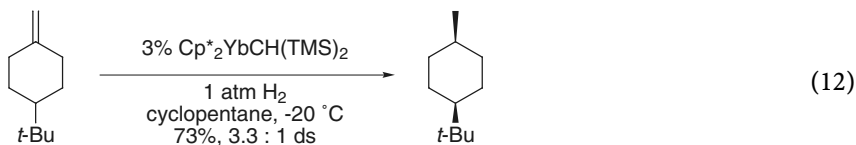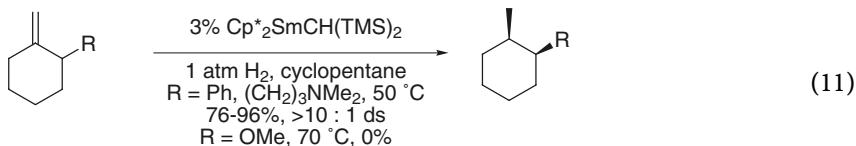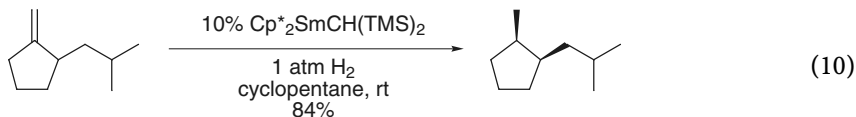
Enantioselective catalytic hydrogenation reactions have been reported and appear to offer synthetically useful results, although for a very limited set of alkenes [10, 26]. Thus deuteration of styrene and hydrogenation of substituted styrenes, molecules with essentially no functional group available to serve as a

stereochemical control element, can be accomplished with modest to high asymmetric induction using a series of elegantly designed chiral, nonracemic catalysts (Eq. 13).

(13)
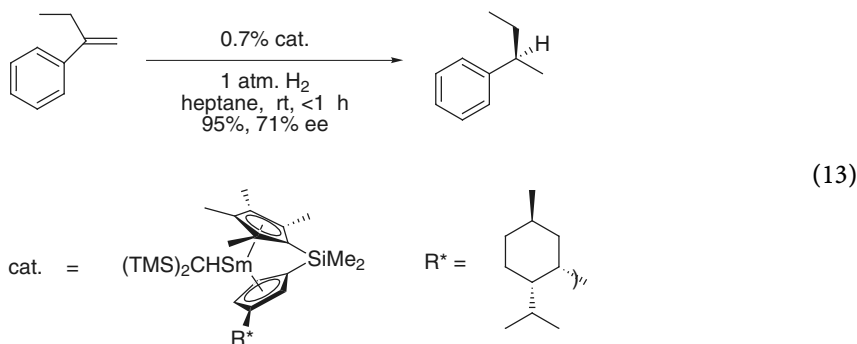
Although a model was proposed in which olefin insertion occurred to place the metal on the terminus of the alkene ("1,2-addition") [10, 26], based upon subsequent mechanistic and synthetic studies of the hydrosilylation reaction of styrenes (see below), this model would appear to be incorrect [27]. Thus an irreversible, stereochemically determinant "2,1-insertion" probably initiates the reaction, with subsequent σ-bond metathesis completing the process. Most remarkable is the fact that, if correct, this model demands that the olefin insertion takes place to orient the highly hindered metal center at a tertiary carbon center, and that apparently little, if any, β-hydride elimination occurs from the resultant organometallic.

A "frontal trajectory" has been suggested to explain the sense of asymmetric induction in these reactions (Fig. 4), and seems most valid based on steric effects. However, a "lateral trajectory" cannot be ruled out based upon the evidence available to date [10, 26].

Alkynes also undergo selective hydrogenation to generate *cis*-alkenes [22, 28]. The process has not been developed, however, and at any rate it is unlikely to compete with more established methods.
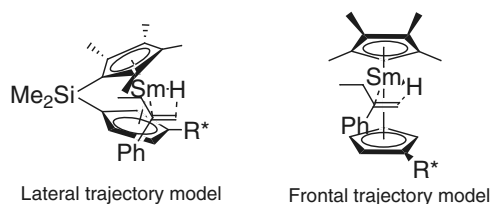

Lateral trajectory model   Frontal trajectory model

Fig. 4. Models for asymmetric induction in hydrogenation of styrene derivatives

4
Catalytic Hydrosilylation Reactions

Metal catalyzed hydrosilylation reactions provide the most efficient and economical route to organosilanes [29]. Organosilanes can be readily oxidized to the corresponding alcohols utilizing a Tamao procedure or related reactions [30]. The overall process thus constitutes the synthetic equivalent of a catalytic hydroboration/oxidation sequence [31]. One advantage of the silylation/oxidation protocol is the stability of the intermediate silane which allows the unmasking of the alcohol to be performed at a synthetically convenient time. In spite of the potential of hydrosilylation reactions in selective organic synthesis, relatively little effort has been made to develop procedures for the selective hydrosilylation of polyfunctional alkenes and alkynes, especially when compared to the analogous hydroboration reaction.

Organolanthanide and group 3 organometallic catalysts provide an alternative to the more traditional platinum-based catalysts for the selective hydrosilylation of alkenes and alkynes. Mechanistically, the transformation is analogous to the catalytic hydrogenation reaction detailed previously [22]. When silane is utilized in place of hydrogen, the σ-bond metathesis occurs to place the silane moiety on the alkyl unit, and the organometallic hydride is again regenerated (Fig. 5). In the overall process a rapid, exothermic, and essentially irreversible olefin insertion is followed by the slower, rate-determining σ-bond metathesis. Because the group 3 metallocenes and organolanthanides are highly effective catalysts for dehydrogenative polysilylation [32], the desired process demands that olefin insertion and σ-bond metathesis occur much more rapidly than the generation of polysilanes.
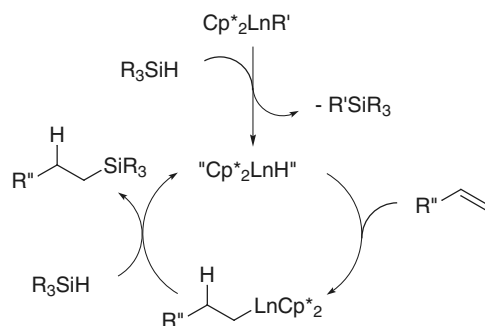

Fig. 5. Catalytic cycle for hydrosilylation

4.1
Silylation of Alkenes

The earliest reported examples of group 3 or organolanthanide catalyzed hydrosilylation reactions emphasized reactions with simple alkenes (e.g., 1-octene) (Eq. 14) [33]. The lutetium- and neodymium-based catalysts utilized for these studies typically required 2 d at high temperatures (80–90 °C) to react and provided modest to good yields of the desired terminal (linear) organosilanes. Styrene provided mixtures of linear and branched organosilanes [Eq. (15)].

$$\tag{14}$$

$$\tag{15}$$
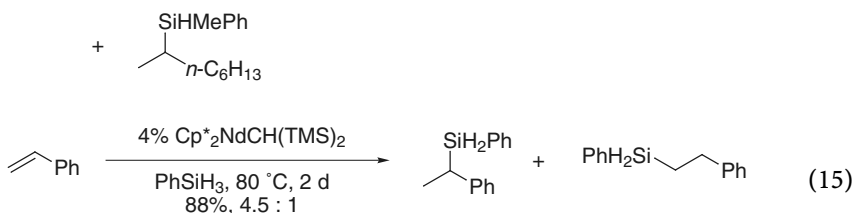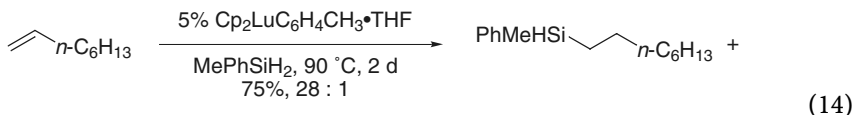
The regioselectivity of olefin insertion varies with the complex used in the reaction [27, 34]. In the hydrosilylation of a monosubstituted olefin, the use of complexes with larger metals and more open ligands provide increased yields of the product derived from reversed ("2,1") insertion (Eq. 16). These results reveal that a variety of complexes give excellent selectivity for terminal insertion, but the conditions to elevate the amount of "2,1" insertion remain elusive.

Catalyst	Yield (% isolated)	ds
Cp*$_2$LuMe•THF	98	100 : 0
Cp*$_2$YbCH(TMS)$_2$	91	100 : 0
Cp*$_2$YMe•THF	84	100 : 0
Cp*$_2$SmCH(TMS)$_2$	90	11 : 1
Cp*$_2$NdCH(TMS)$_2$	85	3.2 : 1
Cp*$_2$LaCH(TMS)$_2$	90	1.9 : 1
Me$_2$SiCp"$_2$YCH(TMS)$_2$	84	31 : 1
Me$_2$SiCp"$_2$SmCH(TMS)$_2$	98	1 : 2
Me$_2$SiCp"$_2$NdCH(TMS)$_2$	89	1 : 2

$$\tag{16}$$
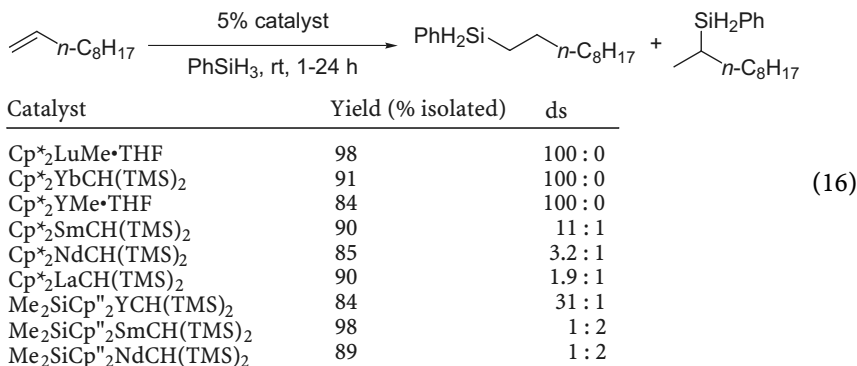
The development of organoyttrium catalysts provided a major breakthrough in terms of efficiency and selectivity in the synthesis of organosilanes [35]. These catalysts reacted with monosubstituted alkenes and reactive disubstituted alkenes within hours at room temperature, providing high yields of the desired

organosilanes (Eq. 17). It was also demonstrated that common organic functional groups (halides, ethers, and acetals) could be tolerated under the reaction conditions (Eq. 18).

$$3\% \ Cp^*_2YCH(TMS)_2$$

PhSiH$_3$, benzene
rt, 3.5 h, 85%

SiH$_2$Ph

(17)

$$3\% \ Cp^*_2YCH(TMS)_2$$

PhSiH$_3$, benzene
rt, 83-96%
X = Cl, OBn, OTBDMS, OTHP

X⁓SiH$_2$Ph

(18)
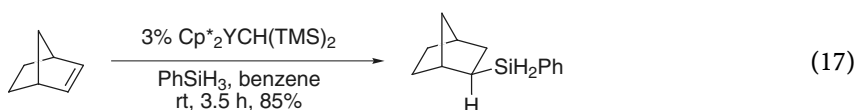
In the same study, remarkable steric selectivity was demonstrated in the hydrosilylation of dienes with varying substitution patterns [35]. Virtually complete selectivity was observed for the reaction of monosubstituted olefins in the presence of disubstituted alkenes (Eqs. 19, 20) and for the silylation of a 1,1-disubstituted olefin in preference to a trisubstituted double bond (Eq. 21).

$$3\% \ Cp^*_2YCH(TMS)_2$$

PhSiH$_3$, benzene, rt
92 h, 91%

SiH$_2$Ph

(19)

$$3\% \ Cp^*_2YCH(TMS)_2$$

PhSiH$_3$, toluene, rt
18 h, 97%

SiH$_2$Ph

(20)

$$3\% \ Cp^*_2YCH(TMS)_2$$

PhSiH$_3$, benzene, rt
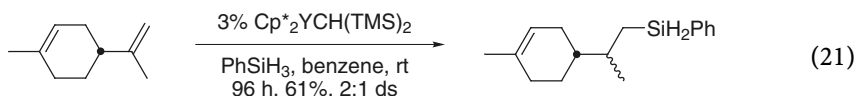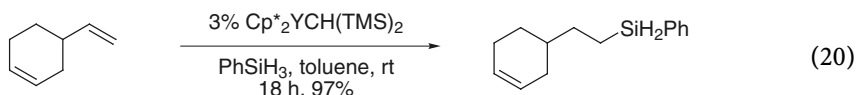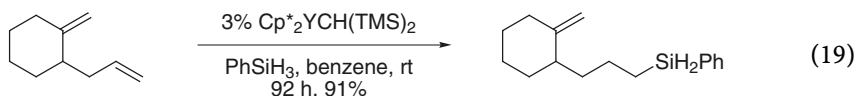96 h, 61%, 2:1 ds

SiH$_2$Ph

(21)

The yttrium catalysts are less effective for more sterically hindered olefins, but the flexibility afforded by being able to alter both the metal and the ligand system provides a means to adjust reactivity in a manner that allows hydrosilylation of more highly substituted alkenes. The simple modification of increasing the ionic radius of the metal permits the hydrosilylation of 1,1-disubstituted alkenes (Eq. 22) [25]. This effect dominates over slight ligand modifications, as a complex with more hindered ligands (C_5Me_4i-Pr) (Eq. 23) shows similar reactivity to the C_5Me_5-derived yttrium complex (Eq. 21) [36]. A silicon-hinged catalyst further increases turnover frequency over nonbridged systems by a factor of eight (Eq. 24) [27]. Unfortunately, there is a trade-off with the more open catalysts. Although increased reactivity with more highly substituted alkenes is observed, monosubstituted alkenes react with poor regioselectivity.

5% Cp*$_2$SmCH(TMS)$_2$

PhSiH$_3$, cyclohexane
70 ˚C, 12 h
63-92%, 9 : 1 ds
R = Me, i-Bu, Bn, (CH$_2$)$_3$NMe$_2$

SiH$_2$Ph

(22)

5% (C$_5$Me$_4$i-Pr)$_2$SmCH(TMS)$_2$

PhSiH$_3$, cyclohexane
rt, 96 h, 82%

SiH$_2$Ph

(23)

cat. Me$_2$SiCp'$_2$SmCH(TMS)$_2$

PhSiH$_3$, benzene-d$_6$
60 ˚C, 98%
Cp' = C$_5$Me$_4$

SiH$_2$Ph

(24)
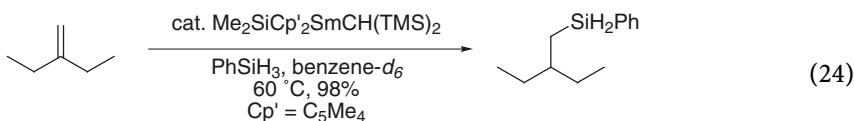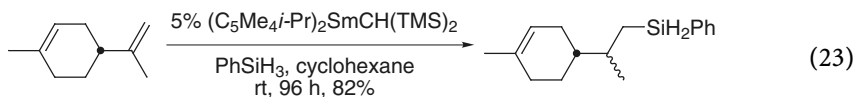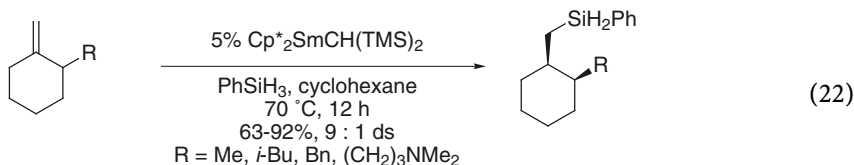
Styrene derivatives react with "2,1-" regioselectivity [27]. This reversal of selectivity varies considerably with the metal ionic radius and the ligand array present, with larger metals and bridged ligands giving higher ratios of the "2,1" product. As with the catalytic hydrogenation of styrene derivatives discussed previously, the olefin insertion reaction defines the regiochemistry and stereochemistry of the final product. Thus the olefin insertion is essentially irreversible under the reaction conditions, and the σ-bond metathesis presumably occurs with retention of configuration to provide the observed products with remarkably high ee's considering the overall nature of the transformation (Eq. 25).

0.5% cat.

PhSiH$_3$, benzene-d$_6$
rt, 98%, 68% ee

SiH$_2$Ph

(25)

cat. = (TMS)$_2$CHSm   SiMe$_2$ R* =

R*
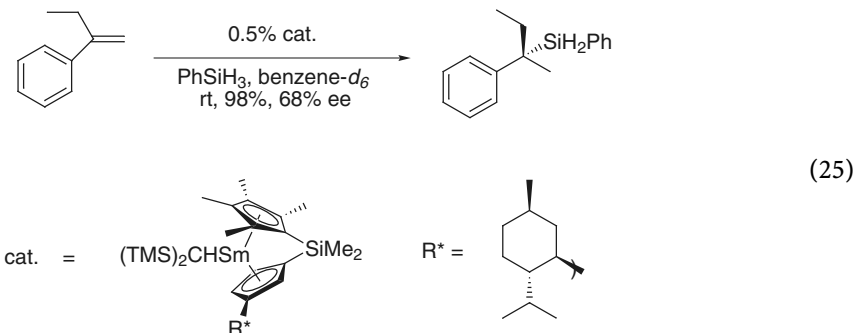
4.2
Silylation of Alkynes

Although terminal alkynes are metallated with organolanthanide hydrides and therefore cannot be hydrometallated [37], internal alkynes do undergo effective hydrosilylation [38]. As expected, *cis*-addition of the organometallic hydride to

the alkyne is observed (Eq. 26). Branching at one of the propargyl positions is necessary for high regioselectivity in unsymmetrical alkynes. A variety of branched substituents are suitable for use (Eqs. 27–31) widening the possibilities of subsequent synthetic steps. Placing a tertiary group on the alkyne (Eq. 30) slows the reaction, allowing the competitive dehydrogenative polymerization of silane to lower the yield of the desired product.

(26)

(27)

(28)

(29)

(30)

$$(31)$$
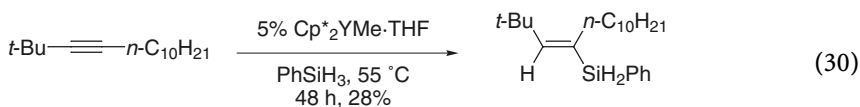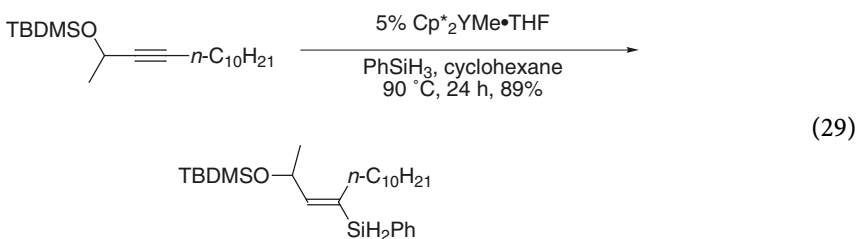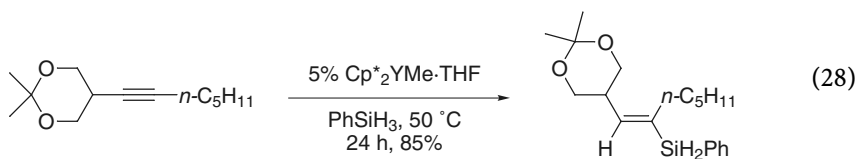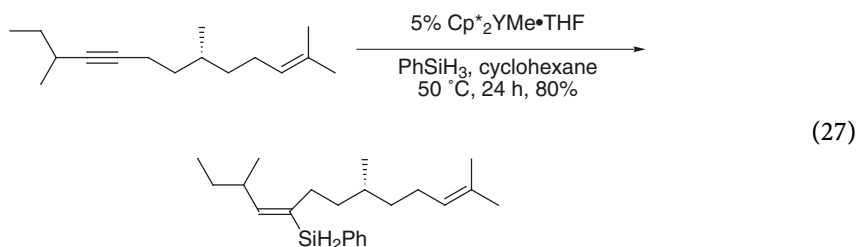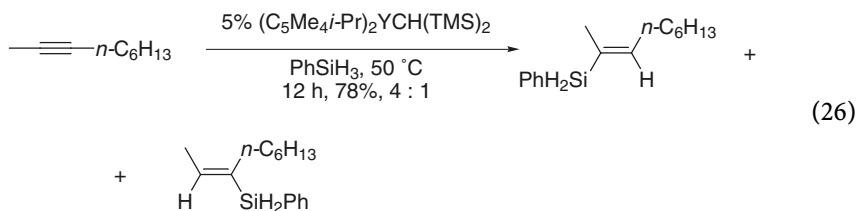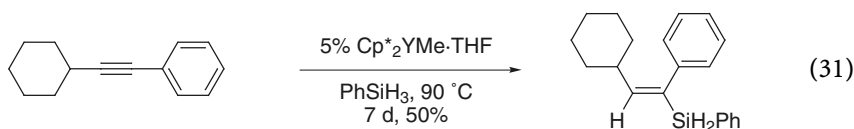
Equation (31) illustrates an interesting facet of this regioselectivity [38]. Although both substituents are branched, the phenyl group is effectively smaller than the cyclohexyl moiety, allowing good selectivity. The steric preference is likely buttressed by the same electronic directing effects of aryl groups observed for styrene derivatives [27].

The critical and in fact rate-limiting step of alkyne hydrosilylation is the σ-bond metathesis [38]. Both the increased strength of a C_{sp2}-metal bond and the geometric requirements for the σ-bond metathesis combine to require the reactions to be heated overnight to achieve high yields of the desired alkenylsilanes. The hydrosilylation of alkynes is tolerant of a wide variety of functional groups (Eq. 32) including halides, amines, and several alcohol protecting groups [38]. A collection of substrates that were unreactive at temperatures up to 90 ˚C is pictured in Fig. 6. The strongly Lewis acidic complexes probably cause catalyst-deactivating ionization of the propargylic acetals.

$$(32)$$
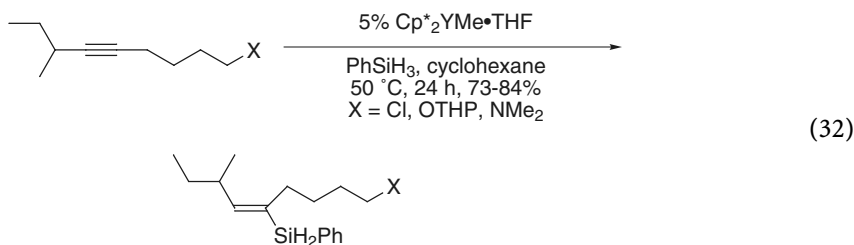
The chemoselectivity of the catalyst for alkynes over alkenes is of interest. Excellent discrimination is achieved in substrates containing an alkyne paired with a hindered olefin (Eqs. 27, 33) [38]. When offered a monosubstituted olefin (Eq. 34) the catalyst is less selective, producing mixtures of alkyl- and vinylsilanes. As previously noted for the hydrogenation of dienes, the addition of a group allylic to the alkene sterically shields the double bond and can electroni-
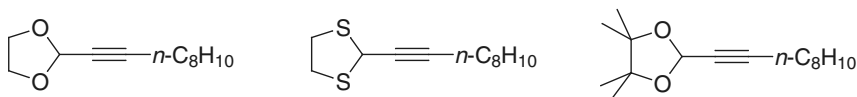
Fig. 6. Alkynes that are unreactive to catalytic hydrosilylation conditions

cally deactivate it as well (Eq. 35). This allows virtually complete selectivity for alkyne insertion.

(33)

(34)

(35)
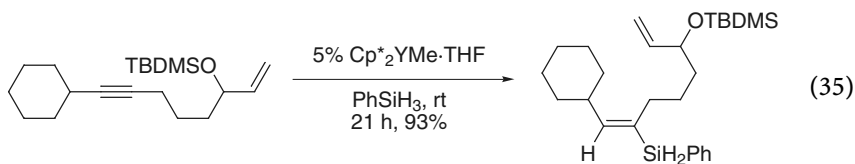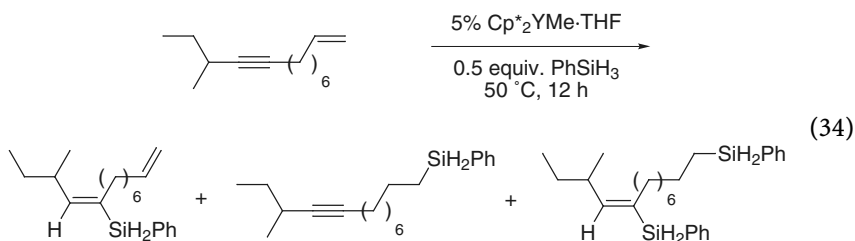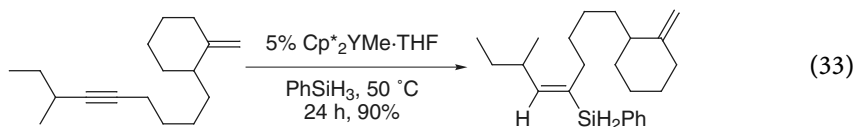
5
Catalytic Cyclization Reactions

The propensity for organolanthanides and group 3 organometallics to undergo olefin insertion reactions leading to the polymerization of α-olefins provides the possibility of cyclizing dienes and other polyunsaturated substrates. A reasonable catalytic cycle for such a transformation is depicted in Fig. 7. There are several requirements for successful cyclization. In an unsymmetrical diene, selective reaction at a single alkene is necessary to avoid a mixture of regioisomeric products. As noted previously, this requirement has been met with organoyttrium catalysts (Eq. 8) [24]. If the reactions are carried out under a hydrogen atmosphere, intramolecular olefin insertion must occur more rapidly than σ-bond metathesis of the newly formed organometallic with hydrogen. Diastereoselectivity is established in the cyclization, and should be predictable based upon a simple chair transition structure for the cyclization. Finally, in the absence of hydrogen the catalytic cycle can be completed by β-hydride elimination to afford the exomethylene-substituted cycloalkane.

Fig. 7. Catalytic cycle for the cyclization of dienes

5.1
Termination by β-Hydride Elimination

Carbocycles and heterocycles ranging from five-membered to nine-membered have been synthesized utilizing organoscandium catalysts (Eqs. 36–39) [8]. These reactions are carried out in the absence of hydrogen or other "chain terminators". Consequently, the organometallic generated after initial olefin insertion is more persistent, and is therefore provided the time to cyclize to ring sizes that are normally inaccessible. Diastereoselectivity issues were not addressed in this study, nor was the tolerance of the catalysts for a wide range of functional groups. From the reported studies it is clear that discrimination of the catalysts for a monosubstituted alkene in the presence of an allylically substituted monosubstituted alkene is not high (Eq. 39).

$$(36)$$

$$5\% \ [DpScH]_2, \ 80\ ^\circ C, \ 10\ min, \ quant \tag{37}$$

$$4\% \ Me_2SiCp'_2Sc(H)(PMe_3), \ 80\ ^\circ C, \ 10\ min, \ 93\% \tag{38}$$

$$6\% \ [DpScH]_2, \ 80\ ^\circ C, \ 10\ min, \ 99\%, \ 2:1 \tag{39}$$
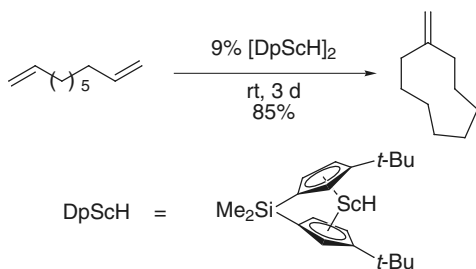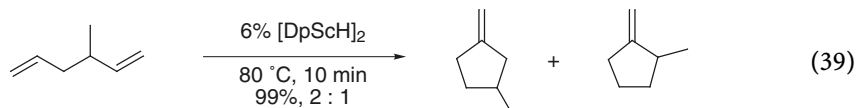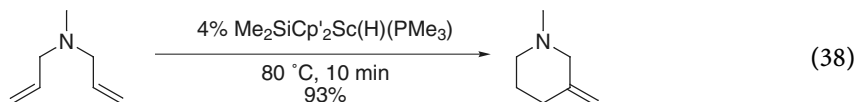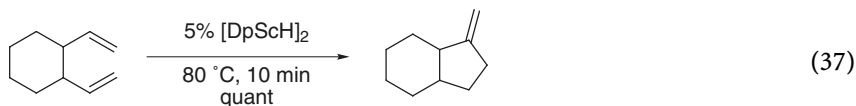
5.2
Termination by Hydrogenation

Organoyttrium catalysts have been utilized to effect the cyclization of dienes under reductive conditions [39]. Excellent selectivity is achieved in these reactions between two monosubstituted alkenes leading to a single regioisomeric product (Eq. 40), and the diastereoselectivity is consistent with the simple chair transition structure model (Fig. 7). Both acetals and thioacetals are tolerated (Eq. 41), whereas nitriles, esters, and sulfones preclude product formation (Eq. 42).

$$5\% \ Cp^*_2YMe{\bullet}THF, \ 1\ atm\ H_2, \ benzene, \ rt, \ <1\ h, \ 99\%, \ 21:1\ ds \tag{40}$$

$$5\% \ Cp^*_2YMe{\bullet}THF, \ 1\ atm\ H_2, \ benzene, \ rt, \ <1\ h, \ X=O, \ 85\%, \ X=S, \ 97\% \tag{41}$$

$$5\% \ Cp^*_2YMe{\cdot}THF, \ 1\ atm\ H_2, \ benzene, \ R = CN, \ CO_2Me, \ SO_2Ph, \ no\ reaction \tag{42}$$
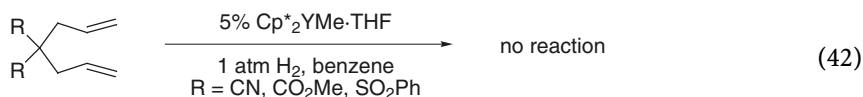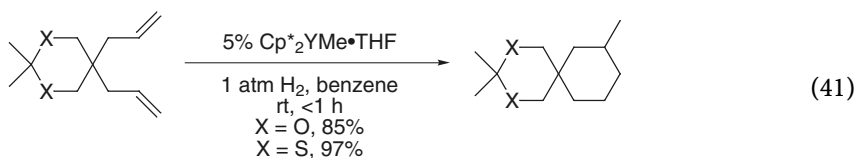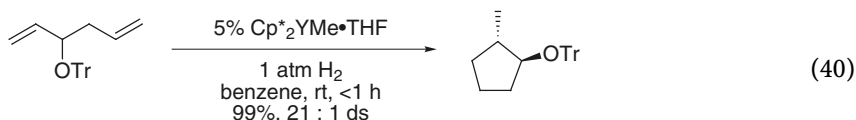
A reduced yield of the cyclized product accompanied by reduced uncyclized material is obtained in the reaction of 1,2-divinylbenzene (Eq. 43) [39]. This could be caused by the rigid aryl group skewing the geometry of the transition

state, making cyclization more difficult. Additionally, it seems likely that a substantial amount of inverse ("2,1") addition occurs. The failure of the secondary benzylic organometallic thus formed to cyclize would lead to formation of the uncyclized hydrogenated product.

$$
\begin{array}{c}
\text{5\% Cp*}_2\text{YMe·THF} \\
\hline
\text{1 atm H}_2\text{, benzene} \\
\text{rt, 1 h}
\end{array}
\qquad
\begin{array}{cc}
53\% & 26\%
\end{array}
\tag{43}
$$
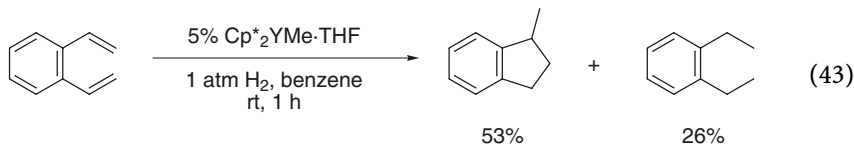
Fully reduced uncyclized material is also obtained in the hydrogenation of diallyldimethylsilane (Eq. 44) [39]. This is undoubtedly because the relatively long Si-C bonds perturb the cyclization transition state.

$$
\begin{array}{c}
\text{5\% Cp*}_2\text{YMe·THF} \\
\hline
\text{1 atm H}_2\text{, benzene} \\
\text{rt, 1 h, 64\%}
\end{array}
\tag{44}
$$
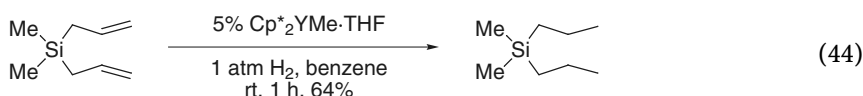
More highly hindered (e.g., 1,1-disubstituted) alkenes cannot be accommodated by the Cp*$_2$YH catalysts. However, more sterically open catalysts permit rapid cyclization under extraordinarily mild conditions (Eq. 45) [10].

$$
\begin{array}{c}
\text{0.5\% cat.} \\
\hline
\text{1 atm H}_2 \\
\text{neat, rt, 2 h}
\end{array}
\tag{45}
$$

cat.   =   (TMS)$_2$CHY—SiMe$_2$ R* =
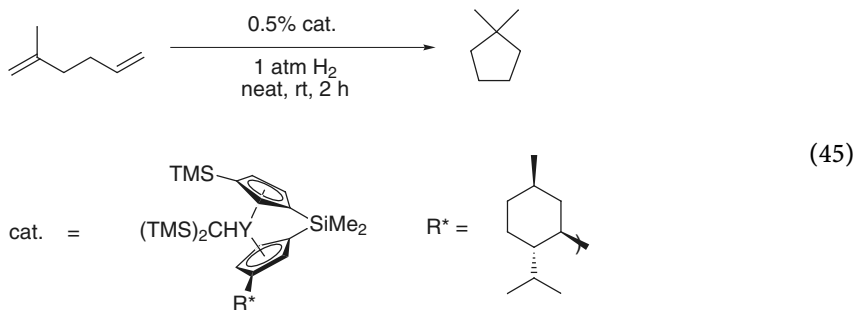
5.3
Termination by Silylation

Although the cyclization reactions described above represent a potentially powerful means for carbon-carbon bond formation, under reductive (hydrogenolysis) conditions the method utilizes a highly functionalized diene substrate and leaves an essentially unfunctionalized product in its wake. The utilization of silylation as a chain terminating event provides a way to place functionality back into the molecule after the cyclization (Fig. 8).
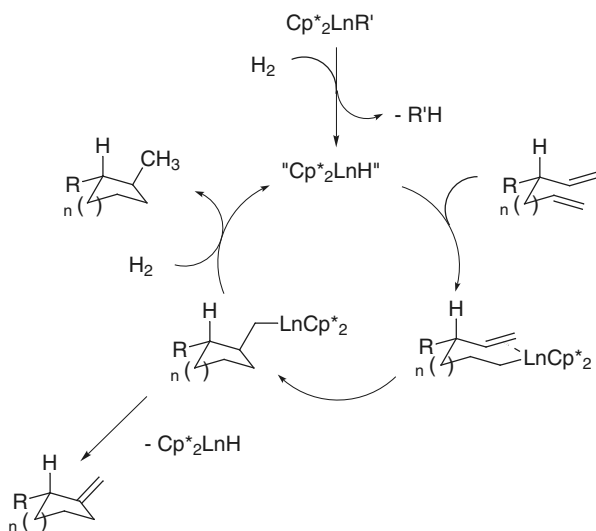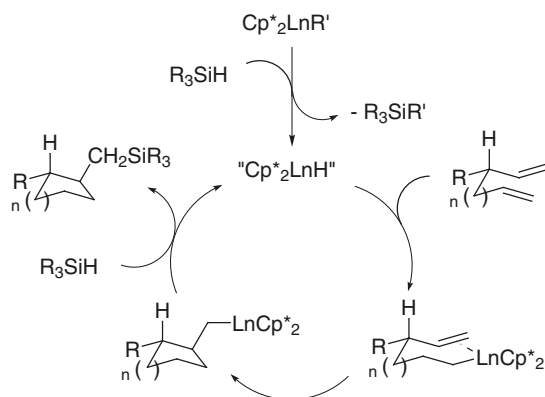
Fig. 8. Catalytic cycle for the cyclization/silylation of dienes

5.3.1
Cyclization/Silylation of Terminal Dienes and Trienes

Early studies centered on the utilization of organolutetiums (Eq. 46) [32a], organoneodymiums [33c], and organosamariums [27] for the cyclization of 1,5-hexadiene and homologs. The early studies of the cyclization/silylation process included only unsubstituted dienes, leaving questions of regioselection, diastereoselection, and functional group toleration unanswered. A more thorough study of this chemistry that focused on the application to small molecule synthesis was performed utilizing organoyttrium complexes [40]. The organoyttrium-catalyzed process employed on monosubstituted dienes appears to be quite general for the synthesis of both five- and six-membered rings. For the synthesis of five-membered rings, phenylsilane is a convenient "chain terminator." It provides high yields of cyclized/silylated products with no stereocenters introduced as a result of the incorporation of the silicon atom. High diastereoselectivities are achieved in many instances (Eq. 47).

$$(46)$$

$$(47)$$
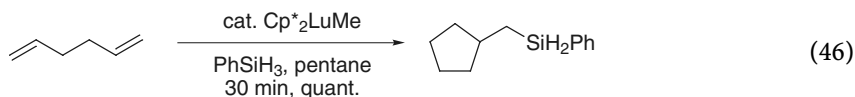
Noteworthy in all of these metallocene-catalyzed reactions is the fact that they proceed with complete "atom economy" [41], i.e., all of the atoms from the sub-

strates and reagents are incorporated into the desired product and there are no byproducts produced. Many of these reactions are so clean, in fact, that pouring the reaction mixture through a short bed of Florisil to remove the catalyst, followed by evaporation of the solvent and bulb-to-bulb distillation, leads to essentially quantitative yields of analytically pure product.

The synthetic equivalency of the silane and an alcohol can be easily demonstrated by subjecting the crude silane product to any of a variety of available oxidizing conditions (Eq. 48) [30, 40].

$$(48)$$

74% overall yield
9 : 1 ds
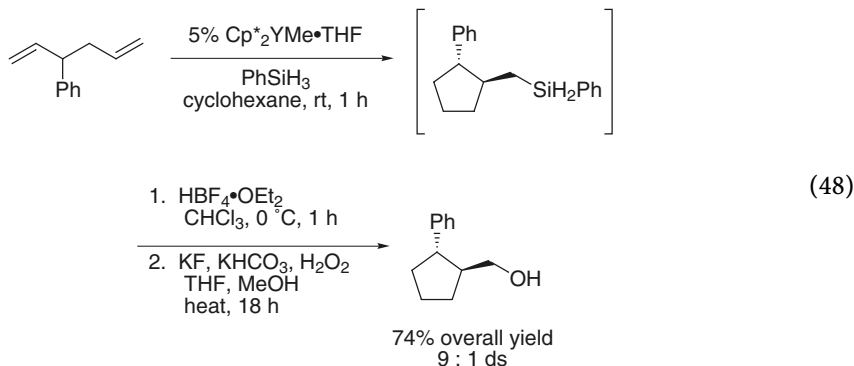
Cyclohexane formation is entropically less favorable than cyclopentane generation, and treatment of 1,6-dienes under the conditions listed in Eq. (47) leads to the production of uncyclized, disilylated products (Eq. 49) [35] or silicon bridged dimers [40]. To avoid these problems, phenylmethylsilane can be employed as the chain terminator. Utilizing this more hindered silane slows the σ-bond metathesis sufficiently to prevent dimerization (Eq. 50). The trapping step can be retarded even further by the use of diphenylsilane (Eq. 51). Thus, not only can the metal and the ligand array be manipulated to bring about the desired result in the catalytic process, but the properties of the silane reagent itself can also be adjusted to meet the demands of the synthesis at hand.

$$(49)$$

$$(50)$$

$$(51)$$
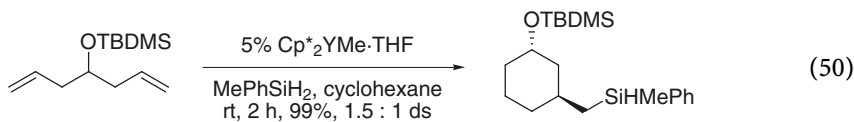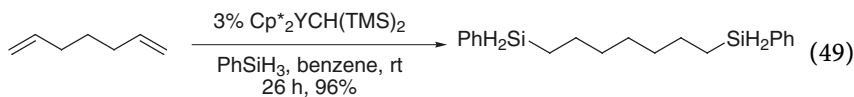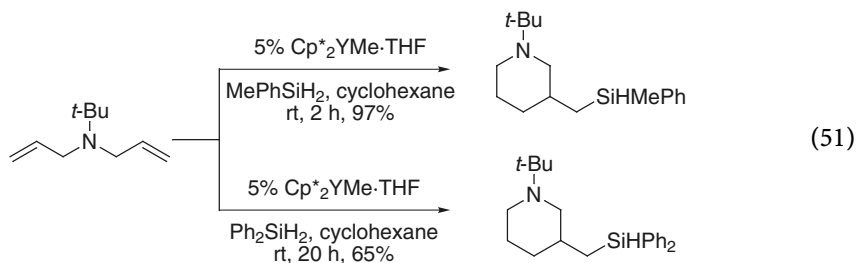
The functional group compatibility of this process is similar to that described previously [40]. Protected alcohols (Eq. 50), tertiary amines (Eq. 51), and protected ketones (Eq. 52) are all inert to the reaction conditions.

$$(52)$$
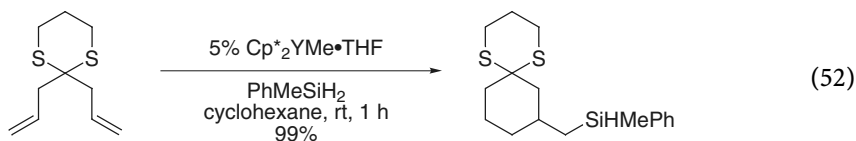
In the reaction of triallylamine (Eq. 53) [40], after the first ring forming event the organometallic is trapped by σ–bond metathesis with the silane instead of undergoing an entropically unfavorable intramolecular olefin insertion to yield a bridged bicyclic structure. The remaining double bond then competes effectively for the catalyst, making the isolation of monocyclic silylated product bearing a free allyl group impossible.

$$(53)$$
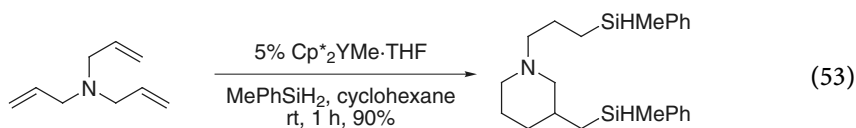
Monosubstituted diene systems have been employed for the synthesis of bicyclic systems as well as monocyclics [17]. The simplest way to accomplish this is to construct a second ring onto an existing structure (Eq. 54). This cyclization process is initiated at the alkene lacking allylic substitution. The formation of the six-membered ring necessitates the use of methylphenylsilane as the silylating reagent. Because the silane itself comprises a new stereocenter, it must be removed by oxidation to assess accurately the diastereoselectivity of cyclization. Fluxionality of the five-membered ring results in a mixture of diastereomers at the silylmethyl-substituted stereocenter.

(54)
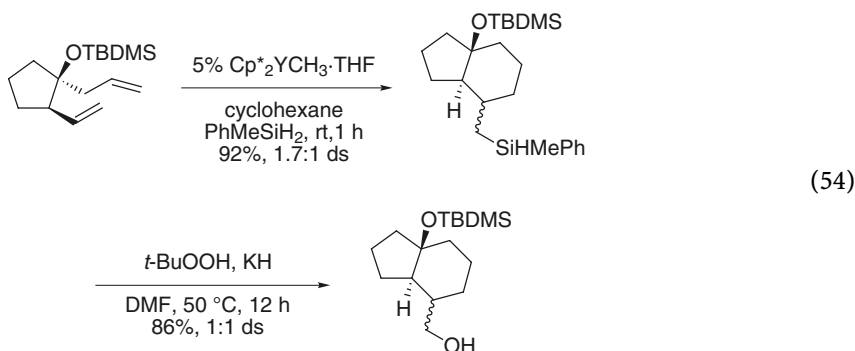
Because the stereochemistry at the ring juncture is passed undisturbed from the substrate, by generating substrates with a fixed relationship between the olefin bearing substituents either ring fusion may be produced at will (Eq. 55) [17]. After oxidation of the silane product and deprotection to the corresponding diol, the stereochemistry of the single isomer was determined by X-ray crystal analysis. In this case the high diastereoselectivity observed may be explained by the transition structures shown in Fig. 9. The bulky organometallic prefers to be away from the existing ring, leading to the observed *cis*-decalin product.

(55)
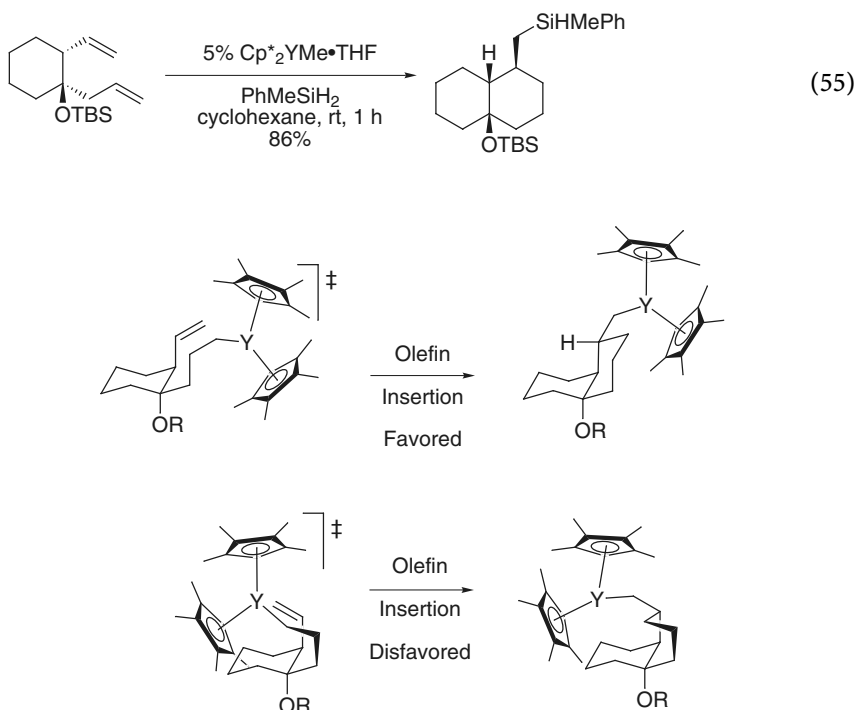
Fig. 9. Steric factors governing *cis*-decalin formation
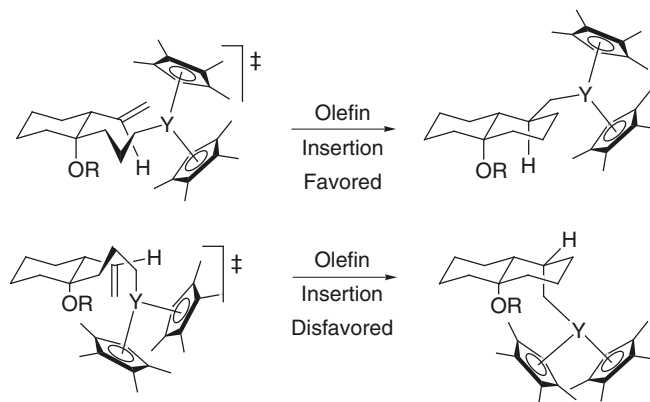
Fig. 10. Steric factors governing *trans*-decalin formation

A *trans*-decalin system can be produced by using a substrate with the opposite diastereomeric relationship (Eq. 56 and Fig. 10) [17]. Of interest is the heightened stereoselectivity observed when the relatively rigid cyclohexane unit is substituted for the fluxional cyclopentane moiety (Eq. 54). This rigidity accentuates the steric interactions governing the stereochemical course of the reaction.

$$(56)$$
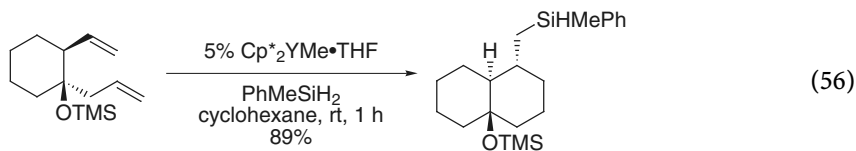
If the substituents are arranged to form a *trans*-decalin with complementary substitution, no cyclization occurs (Eq. 57) [17]. The slower six-membered ring formation at the hindered alkene is interrupted by silylation. This allows impressive chemoselectivity in polyene substrates. When presented with a substrate possessing three monosubstituted olefins with varying steric environments, the catalyst can select the least hindered alkene for initial insertion and will only cyclize onto the less hindered of the two remaining double bonds (Eq. 58). A mechanistic outline and depiction of the steric environments is given in Fig. 11.

$$(57)$$
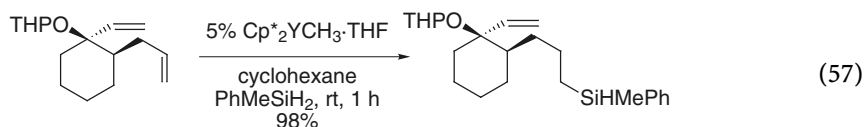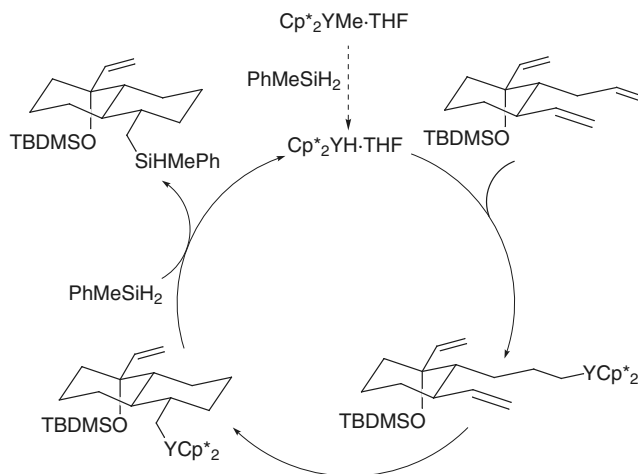
Fig. 11. Catalytic cycle for the selective reaction of a triene
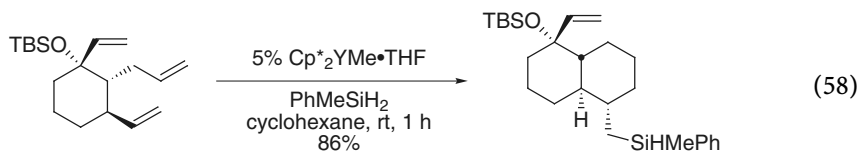
The failure to insert quaternary vinyl groups in a cyclization process is limited to 1,6-diene systems [17]. When a similar competition for selective insertion is attempted on a 1,5-diene, cyclization occurs because of the inherent entropic advantage of five-membered ring formation (Eq. 59). The close approach of the bulky organometallic to the axial alkoxy substituent in the chair-like transition structure (Fig. 12b) causes the reaction to proceed through the less hindered boat formation (Fig. 12a).
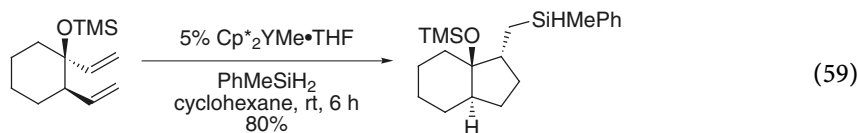
In addition to their ability to assemble bicyclic structures on a monocyclic scaffold, the organoyttrium catalysts can also convert trienes to bicyclics in a sequential process (Eqs. 60, 61) [17]. Both five- and six-membered rings can be constructed at will. In these cases the stereochemistry at the bridgeheads is a result of the chair-like transition structures operative during the intramolecular olefin insertions (Schemes 1, 2). There are two notable features of this reaction. The first is that after the initial olefin insertion a 5-exo cyclization at the allyli-
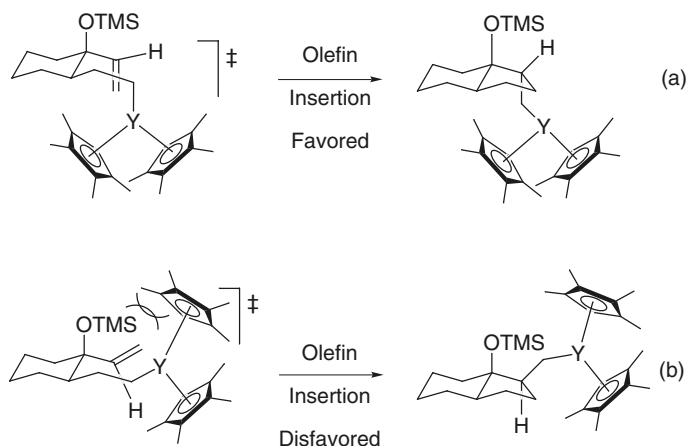
Fig. 12. Steric factors governing bicyclic product formation

cally substituted alkene is chosen over a 6-exo cyclization at an unhindered alkene. The second is the formation of the *trans*-bicyclo[3.3.0] ring system. Currently, the number of methods available to prepare this highly strained system is quite limited [42]. The formation of single product isomers attests to the high chemo- and stereoselectivity of each individual reaction step.

(60)

(61)
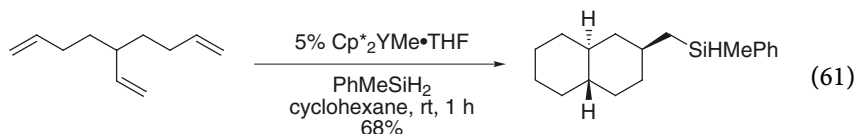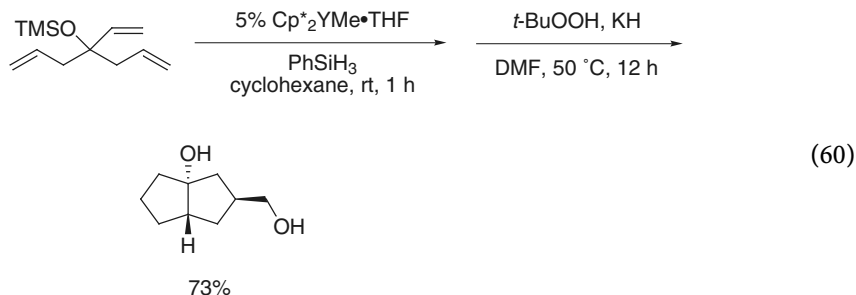
The chemoselectivity of these catalysts allows the selective construction of bicyclic systems bearing additional substitution (Eqs. 62, 63) [17]. By varying the stereochemistry of the substituents, the three-dimensional structure of the product can be altered as desired.

Scheme 1

Scheme 2

(62)

(63)
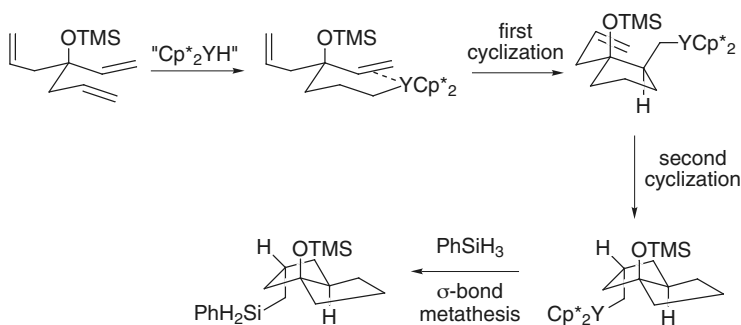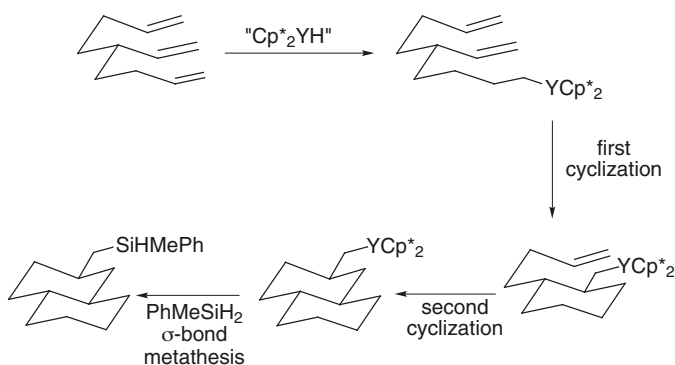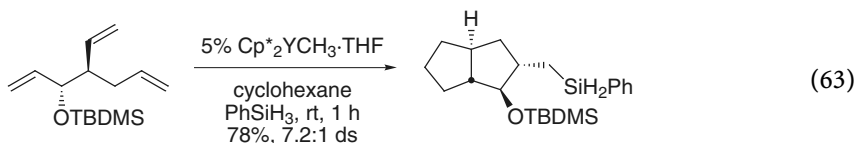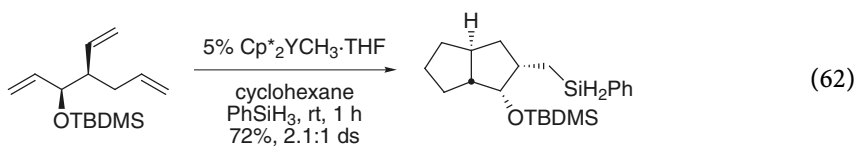
In spite of their recognized Lewis acidity and the propensity to complex with Lewis bases (particularly in an intramolecular chelate) [8], the organoyttrium complexes can be utilized for the synthesis of nitrogen heterocycles. The protocol has been employed in a concise synthesis of (±)-epilupinine (Scheme 3) [43].
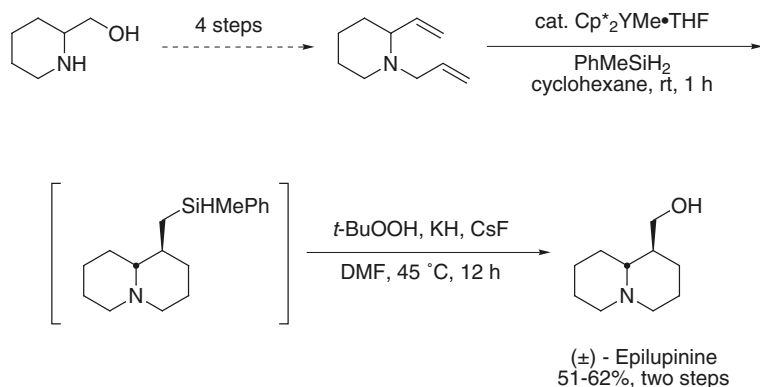
Scheme 3

5.3.2
Cyclization/Silylation of Hindered Dienes and Trienes

As mentioned previously, more highly hindered alkene systems cannot be accommodated by the relatively closed organoyttrium catalysts, and thus more open ligand arrays have been enlisted to allow incorporation of 1,1-disubstituted alkenes. A first generation catalyst was developed that worked quite well in these systems, albeit at somewhat elevated temperatures and protracted reaction times [44]. The ligand possessed a silicon hinge that served to open the clamshell comprised of the cyclopentadienyl rings, and the rings themselves possessed a single trimethylsilyl group to prevent hydride dimer formation. Monosubstituted alkenes reacted in preference to 1,1-disubstituted alkenes (Eq. 64). Remarkably, both alkenes can be disubstituted, generating a quaternary center with complete stereochemical control (Eq. 65). Trienes reacted in a sequential process, in one case leading to a spirocyclic system (Eq. 66).

(64)

(65)

$$5\% \; Me_2Si(Cp^{TMS})_2YCH(TMS)_2$$

$$\overline{PhSiH_3, \text{ cyclohexane}}$$
$$90\ ^{\circ}C,\ 24\ h,\ 64\%$$

$$\text{(66)}$$

SiH$_2$Ph
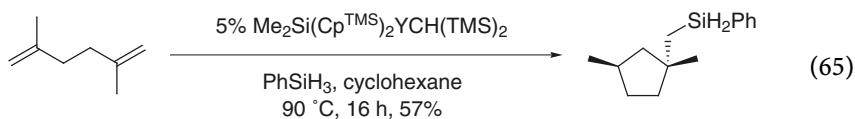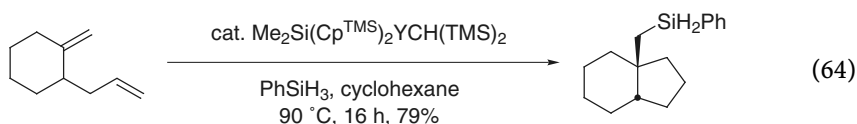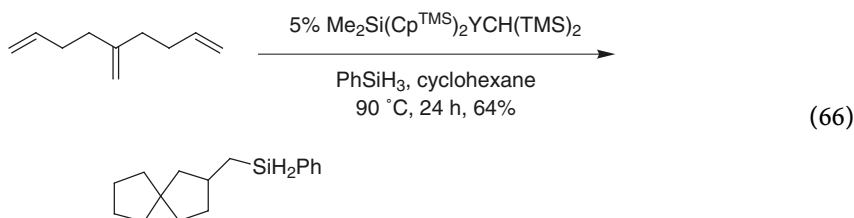
Recognizing the need to carry out these reactions under milder conditions, a second generation catalyst was tested in similar systems [44]. This new system, lacking the silicon hinge, proved to be extraordinarily reactive, in fact orders of magnitude more reactive than any other neutral catalyst tested to date in similar substrates (compare Eqs. 66, 67). As described previously, the precatalyst has modest air stability, and yet the catalyst itself is remarkably reactive. Catalyst loadings as low as 0.5 mol% have been employed in reasonably large scale reactions (10–20 mmol), and the catalyst also supports the presence of the standard functional groups for this general class of catalysts (Eq. 68). One problem with the catalyst is that it apparently becomes deactivated over time because of hydride dimer formation. Ideal reaction conditions for slow-reacting substrates thus involve addition of smaller portions of the catalyst at fixed intervals to maintain an active concentration of the catalyst.

$$5\% \; [(Cp^{TMS})_2YMe]_2$$

$$\overline{PhSiH_3, \text{ cyclohexane}}$$
$$rt,\ 1\ h,\ 88\%$$

SiH$_2$Ph

$$\text{(67)}$$

OTBDPS

$$5\% \; [(Cp^{TMS})_2YMe]_2$$

$$\overline{PhSiH_3, \text{ cyclohexane}}$$
$$rt, 16\ h,\ 74\%$$

OTBDPS

SiH$_2$Ph

Me

$$\text{(68)}$$
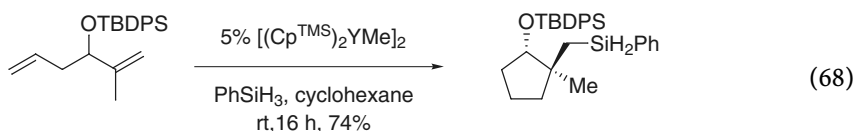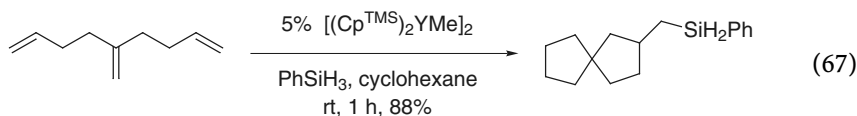
The expanded capabilities of this catalyst allowed the construction of additional ring systems [44]. A transannular olefin insertion formed a bicyclo[3.3.1]nonane structure (Eq. 69). Multiple insertion steps can selectively transform a monocyclic substrate into a propellane derivative (Eq. 70). The catalytic cycle begins at the monosubstituted olefin, followed by the insertion of the remaining double bonds to form five membered rings.

$$5\% \; [(Cp^{TMS})_2YMe]_2$$

$$\overline{PhSiH_3, \text{ cyclohexane}}$$
$$rt,\ 20\ h,\ 50\%$$

SiH$_2$Ph

$$\text{(69)}$$

$$5\% \ [(Cp^{TMS})_2YMe]_2$$

PhSiH$_3$, cyclohexane
rt, 1 h

75%

SiH$_2$Ph

+

(70)

SiH$_2$Ph

+

14%
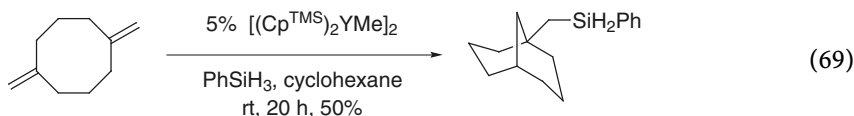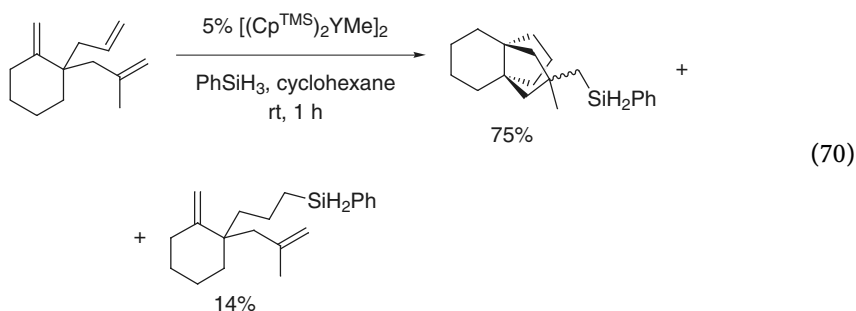
This catalyst is surprisingly intolerant of branching on the hindered olefin (Eq. 71) [44]. The addition of two methylene units between the alkene and the branch point is required to provide good yields of cyclized product. Another limitation is the inability of the complex to insert an endocyclic olefin (Eq. 72).

$$5\% \ [(Cp^{TMS})_2LnMe]_2$$

PhSiH$_3$, cyclohexane
rt, 1 h

n = 0, Ln = Lu
n = 2, Ln = Y

SiH$_2$Ph

+

0%
84%

(71)

PhH$_2$Si

+

84%
0%

$$5\% \ [(Cp^{TMS})_2LuMe]_2$$

PhSiH$_3$, cyclohexane
rt, 1 h, 93%

SiH$_2$Ph

(72)
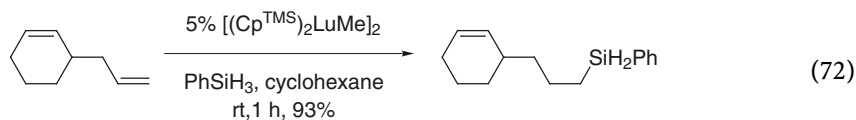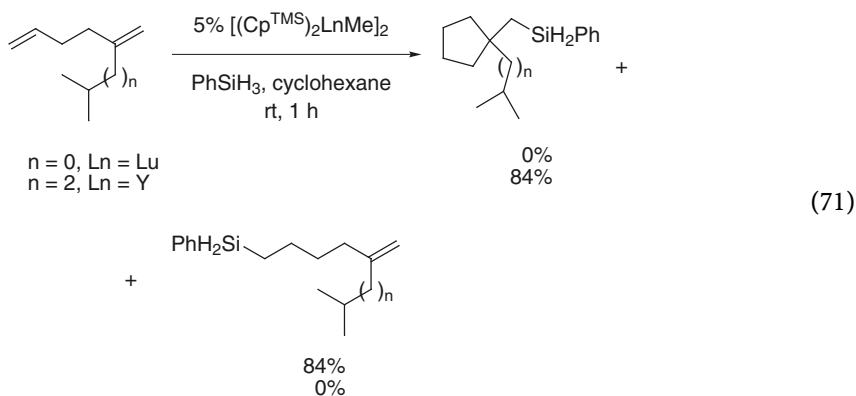
5.3.3
Cyclization/Silylation of Enynes and Dienynes

Enynes have been found to be excellent substrates for the cyclization/silylation sequential reaction [45]. The electron rich alkyne undergoes preferential reaction, thus requiring propargyl branching to direct the regiochemistry of the initial insertion. Although sp^2 hybridized, the organometallic originally formed is converted smoothly via the cyclization/silylation process to afford the desired

products. A variety of functional groups can be tolerated at key positions in these substrates (Eqs. 73, 74). The diastereoselection varies reliably with the size of the substituent, as would be expected from the chair-like transition structure for insertion. Six-membered rings can also be generated in high yields and with modest diastereoselection when phenylmethylsilane is employed (Eq. 75). In this case varying the silylating reagent causes a drastic change in the outcome of the reaction (compare with Eq. 35).

(73)

(74)
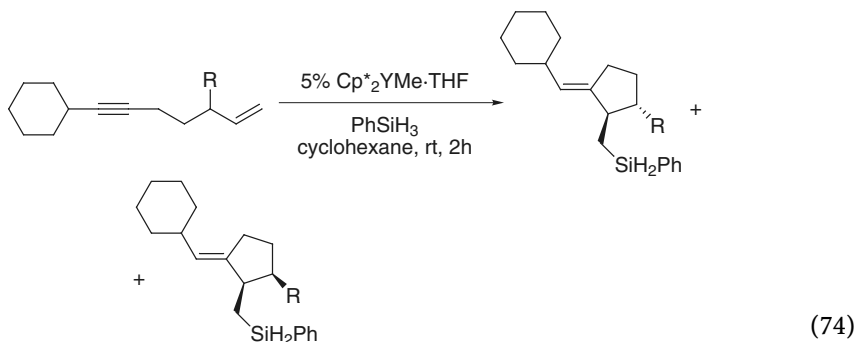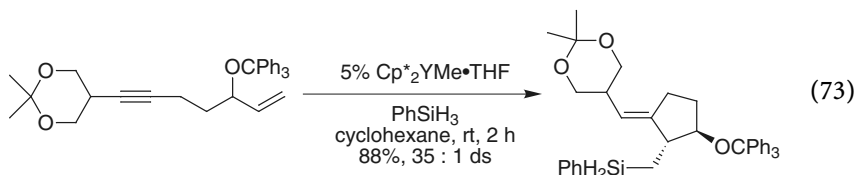
R	% Yield	ds
OTBDMS	93	6.5 : 1
OTIPS	93	12 : 1
OTr	84	24 : 1
Et	88	>50 : 1
CH$_2$OMe (100 ˚C)	80	20 : 1
CH$_2$OTBDMS	76	>50 : 1
—N (isoindoline)	91	40 : 1

(75)
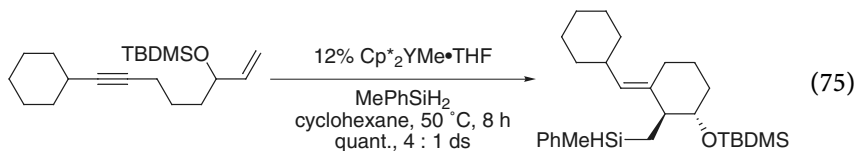
The cyclization protocol can be carried a step further by judiciously placing another olefin in the substrate [38]. The incorporation of an additional allylic group only results in low yields of bicyclic products (Eq. 76). The reduced yield

is undoubtedly because of the poor chemoselectivity between the alkyne and the allylic olefin. Alkyl substitution on the allyl group gives complete selectivity for initial alkyne insertion, but the hindered olefin prevents bicyclic product formation (Eq. 77). Geminal dimethyl substitution at the allylic position, however, provides selectivity in the initial insertion without stopping the second intramolecular insertion from taking place (Eq. 78). This dienyne cyclization allows another entry into the strained *trans*-bicyclo[3.3.0]octane system, and contains an additional handle for further functionalization.

$$\text{5\% Cp*}_2\text{YMe•THF}$$
benzene-d_6, PhSiH$_3$
rt, 2.5 h, 33% (76)

$$\text{5\% Cp*}_2\text{YMe•THF}$$
benzene-d_6, PhSiH$_3$
rt, 24 h, 84% (77)

$$\text{5\% Cp*}_2\text{YMe•THF}$$
benzene-d_6, PhSiH$_3$, rt
18 h, 76%, 3.9 : 1 ds (78)
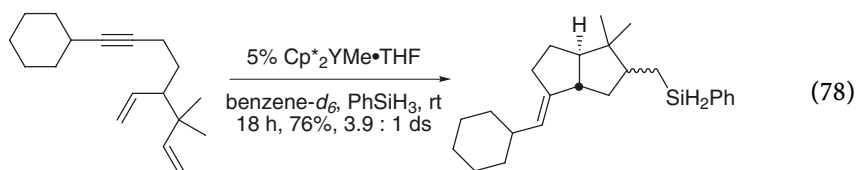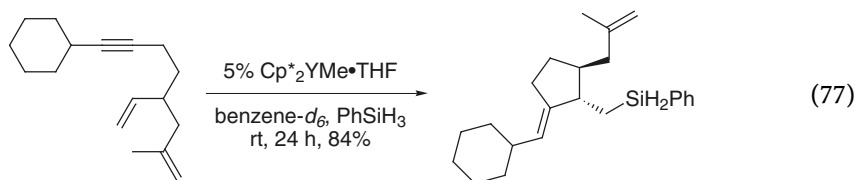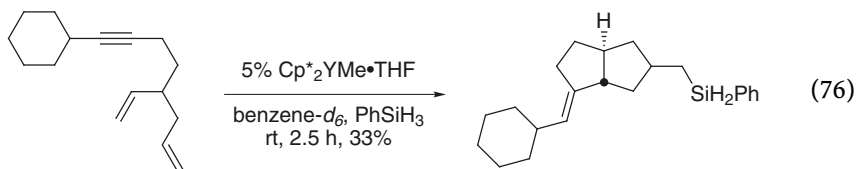
A single substituent allylic to the monosubstituted olefin is sterically large enough to make the initial insertion selective (Eqs. 79, 80) [38]. Either substrate diastereomer can be prepared, leading to different steric interactions in the transition states (Figs. 13, 14), and different product stereochemistry patterns.

$$\text{5\% Cp*}_2\text{YMe•THF}$$
benzene-d_6, PhSiH$_3$
rt, 90%, >40 : 1 ds (79)
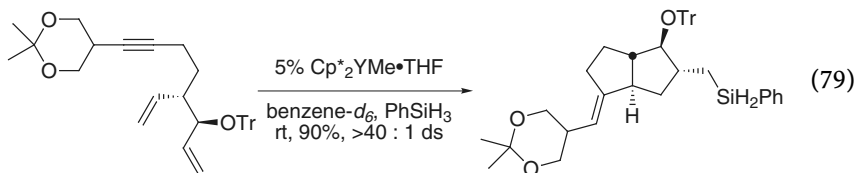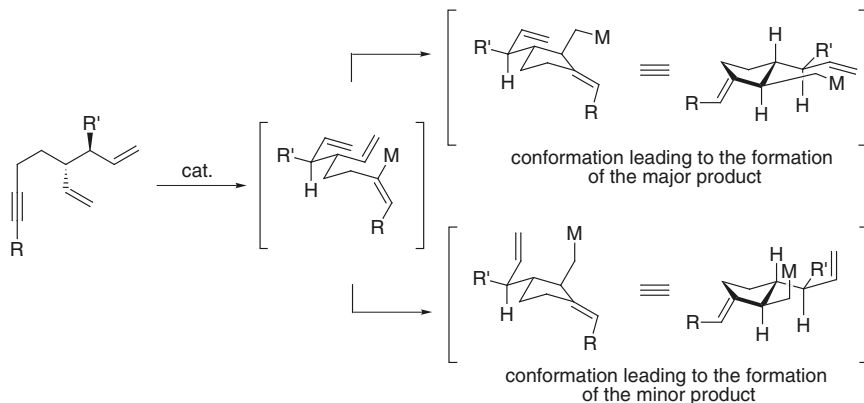
Fig. 13. Steric factors governing dienyne bicyclization
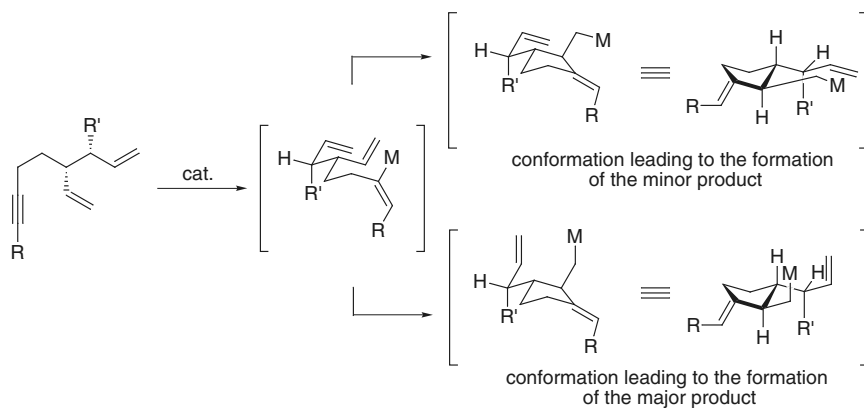
Fig. 14. Steric factors governing dienyne bicyclization

$$\text{(80)}$$
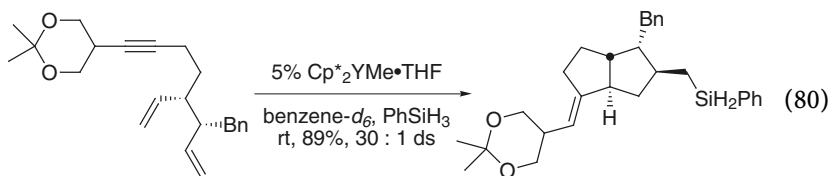
If the alkyl chain is shortened by one carbon, a substrate is generated that has the possibility for bicyclo[2.2.1]heptane generation (Eq. 81) [38]. After the initial alkyne insertion, the catalyst must choose between cyclobutane and cyclopentane formation. The five-membered ring is formed because of the lower

strain involved, but the remaining olefin is not inserted because the lowest energy conformation of the organometallic intermediate places the olefin out of reach of the carbon-metal bond (Eq. 82).

$$\text{(81)}$$

$$\text{(82)}$$
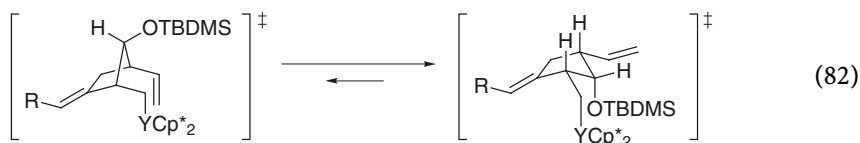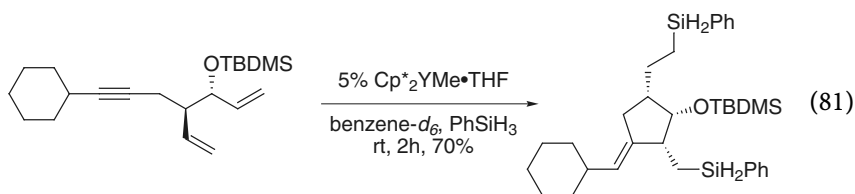
6
Conclusions

The lanthanide- and group 3 metallocenes exhibit a rich chemistry that can be exploited for the selective synthesis of small molecules. At least one class of catalysts that are easily synthesized in a single pot exhibit reasonable stability in the air. Consequently, they should be readily accessible to practicing synthetic organic chemists. Catalysts have been developed that permit reactions of mono-substituted and 1,1-disubstituted alkenes, as well as internal alkynes. Practical solutions for the inability of more highly substituted alkenes to insert have yet to be reduced to practice. Terminal alkynes are rapidly metallated by these catalysts, and are unlikely to be adaptable to many of the processes outlined in this contribution. A variety of functional groups are tolerated by the catalysts (halides, acetals, thioacetals, ethers, and amines), and thus highly functionalized substrates of interest in complex molecule synthesis should be amenable to utilization in selected processes. A high degree of chemoselectivity can be achieved in polyunsaturated systems, and regiochemistry in the olefin insertion reactions can also be controlled. Both of these conspire to provide an effective means to control the direction of cyclization in unsymmetrical systems. Excellent diastereoselectivity can often be achieved, taking advantage of both the inherent selectivity of the catalysts themselves as well as the highly ordered transition structures involved in the intramolecular processes they promote. Finally, elegant asymmetric catalysts have been synthesized and utilized in selective reactions. Further developments in this arena are certain to produce a class of readily available catalysts that provide rapid and efficient entry to a wide range of complex structures in enantiopure form.

7
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Influence of Solvents or Additives on the Organic Chemistry Mediated by Diiodosamarium

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The reactivity of diiodosamarium in solvents other than THF or in mixtures of solvents are discussed. The influence of additives able to coordinate to samarium are then considered (amides, amines or ethers). Proton donors sometimes drastically modify the selectivity of reactions induced by diiodosamarium; some metal salts [such as Fe(III) or Ni(II)] in catalytic amounts may also strongly accelerate or modify reactions induced by diiodosamarium. Thanks to the above tuning of the diiodosamarium reactivity, rich and diversified organic transformations have been performed, some examples of which are presented.

1
Introduction

Diiodosamarium was prepared for the first time by Matignon and Cazes in 1906 by heating triiodosamarium at high temperature under an atmosphere of hydrogen [1]. For a long time, subsequent preparations used high temperature technology and solid state chemistry (for example, see [2]).

   In 1977 we described the mild preparation of diiodosamarium at room temperature by reaction between samarium powder and 1,2-diiodoethane in THF [3]. The dark-green solution of SmI_2 in THF (0.1 M) was used as a convenient reducing agent. We reported in 1980 the basic organic transformations induced by this new reagent [4]. Since that time we, as well as many other groups, have discovered plenty of new reactions, often performed under smooth conditions and with a high selectivity, through a combination of radical and organometallic chemistry. Diiodosamarium is becoming a major reagent in organic chemistry, many reviews on its reactivity are available (for example, see [5–12]). In this article we shall discuss the various ways to tune the reducing properties of diiodosamarium by changing THF to another solvent or by introduction of various additives which can coordinate to samarium or act as catalysts (for a short review, see [13]).

2
Influence of Solvents

2.1
Tetrahydrofuran (THF)

The chemistry of diiodosamarium has been developed in THF mainly because the mild preparation of SmI_2 from samarium powder and 1,2-diiodosamarium

is performed in THF to give stable solutions (under inert atmosphere) of the re-agent [3,4,14]. During the period 1977–1986, the basic organic transformations induced by SmI_2 involved reactions in THF. In 1987 Inanaga et al. described the acceleration of SmI_2-mediated reactions by addition of some HMPA (usually 5%) in THF [15,16]. This effect is discussed in Sect. 3. It involves the coordinat-ing properties of HMPA towards Sm(II) and Sm(III) ions. Another way to alter the redox properties of the Sm(II)/Sm(III) couple is to replace THF by another solvent. One method is to evaporate THF and to add the desired solvent. This ap-proach has been used to prepare SmI_2 complexed by various nitriles (vide infra). The difficulty comes from the necessity to fully remove the last THF molecules which remain bound to SmI_2, and which may influence its reactivity [17]. The best strategy, therefore, is to try to generate SmI_2 directly in the desired solvent. This has been achieved successfully in nitriles, in tetrahydropyran (THP), in tet-raglyme and even in benzene. There are several incentives for performing SmI_2-induced chemistry in various solvents. One can expect some of the following consequences:

1. Acceleration of some reactions,
2. An improved selectivity,
3. New reactions, and
4. Elimination of by-products generated from competitive reactions with THF (H-abstraction, ring opening, etc.).

2.2
Tetrahydropyran (THP)

In 1992, Ito et al. reported the possibility of replacing THF by tetrahydropyran (THP) in some reactions induced by SmI_2 [19,20]. These authors wanted to pre-pare carbanions α to an amino nitrogen, through the strategy depicted in Scheme 1. The reactions were performed in the mixture THP/HMPA, since the
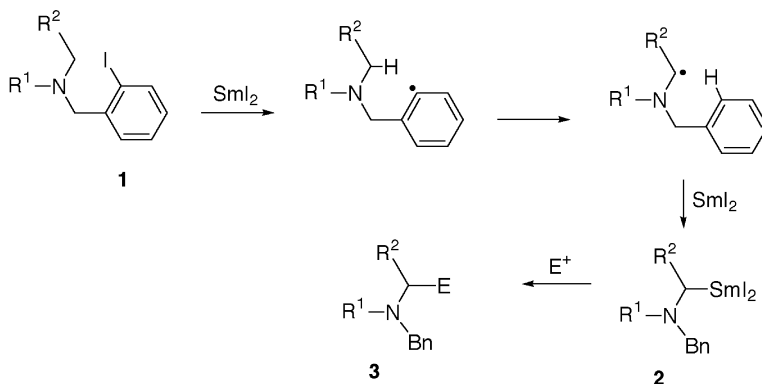
Scheme 1

yields were slightly better than in THF which acts as an intermolecular hydrogen donor to the aryl radical. The appended orthoiodobenzyl in **1** thus generated organosamarium **2** which then produced *N*-benzyl amines **3** by reaction with various electrophiles. SmI$_2$ was directly prepared in THP. Undheim et al. applied this reaction to the alkylation of saturated heterocycles α to nitrogen [21].

In 1994 we set up independently a preparation of SmI$_2$ in THP from samarium metal and 1,2-diodoethane [22]. We wanted to explore the possibility of improving the yields of the acid chloride chemistry, where by-products arise by ring opening of THF. Indeed there was a complete absence of the above by-products. Interestingly, acid chlorides with a branched α-carbon react with SmI$_2$ to give stable THP solutions of acylsamariums **4** which can then react with an aldehyde or ketone to give the mixed α-ketols **5** (Scheme 2). This two-step process avoids the competitive pinacol formation, especially fast when an aldehyde is in the presence of SmI$_2$. Some examples are indicated in Scheme 2. The acylsamarium structure **4** is well supported by the formation of deuterated aldehyde **8**, by reduction of acid chloride **7** and by reaction with D$_2$O.
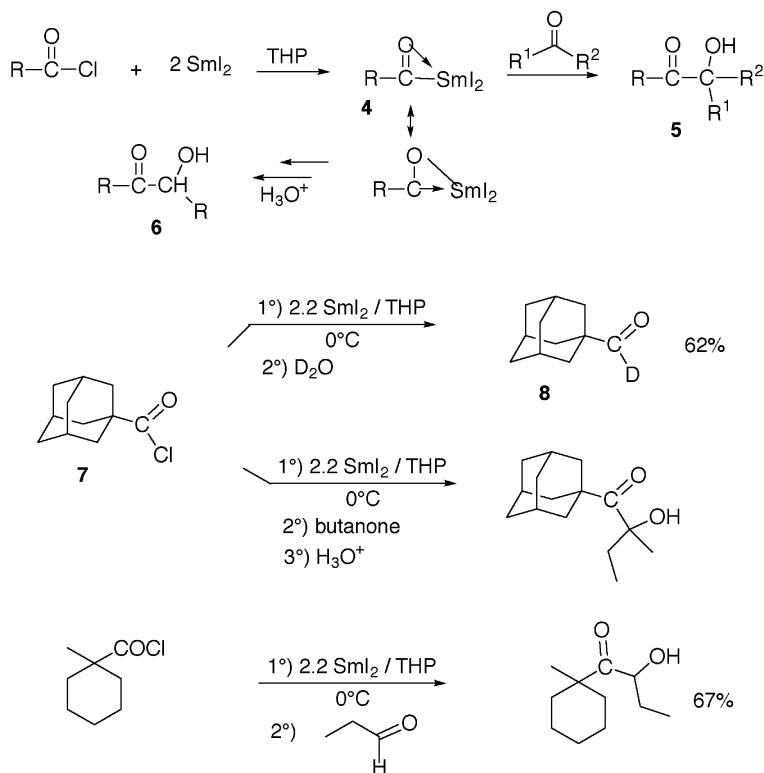
Scheme 2

Acid chlorides with an α-carbon with at least one hydrogen are prone to give self-coupling to symmetrical α-ketols **6**. However, the Barbier procedure in THP allows the preparation of mixed α-ketols **5** in good yields even when using aldehydes.

Recently we discovered that allylic and benzylic samarium compounds could be generated in THP [23]. For example, allylic iodide **9** treated at –15 °C with a THP solution of SmI$_2$ (2 equiv) followed by addition of butanone at the same temperature gave in 90% isolated yield homoallylic alcohol **10** devoid of the usual branched isomer (Scheme 3). Treatment of the allylic organosamarium with D$_2$O provided a fair yield of deuterated alkene. Allylsamarium itself is smoothly prepared at 0 °C and reacts with various types of substrates. Especially interesting is the high *endo* stereoselectivity of addition to camphor, the allylation of imine **11** and the addition on β-keto ester **12** which is easily enolizable. Diiodobenzylsamarium may be prepared at –15 °C from benzyl bromide and reacts with 2-octanone to give the tertiary alcohol in good yield.

In conclusion, THP may in many cases improve the efficiency of reactions initially performed in THF and stabilize organosamarium species which are generated and which may subsequently react with various electrophiles.
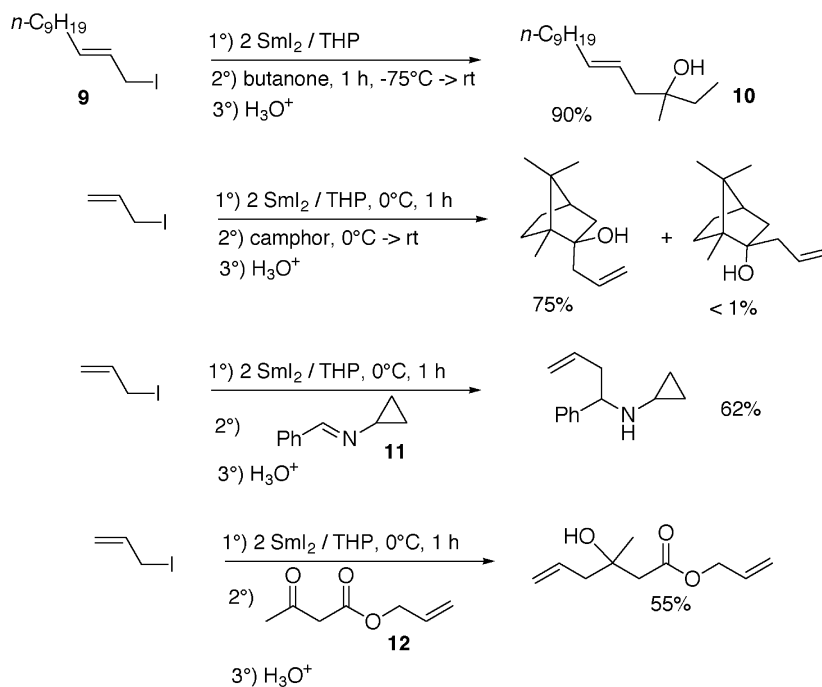
Scheme 3

2.3
Ethers Other Than THF or THP

There are almost no reports of preparation of SmI_2 in ethers other than THF or THP. Inanaga et al. prepared SmI_2 in 1,3-dioxolane and then added 10% acetonitrile to produce a clear solution. This solution was used in the masked formylation of aldehydes or ketones in the presence of iodobenzene [24]. Iodobenzene is transformed into the benzene radical which generates the 1,3-dioxolanyl radical. The latter is presumably reduced to the corresponding organosamarium which then adds on the carbonyl. This process is illustrated in Scheme 4 for cyclododecanone. It is essential to avoid the presence of THF which will compete with 1,3-dioxolane as a hydrogen donor to the benzene radical.

Tetraglyme (2,5,8,11,14-pentaoxapentadecane) has been used in the hydroxymethylation of aldehydes via addition of benzyl chloromethyl ether in the presence of SmI_2. Addition of tetraglyme suppresses the competitive pinacol formation, presumably by a complex formation with SmI_2 as evidenced by a purple color [25]. Tetraglyme has also been used as a cosolvent in an intramolecular Barbier reaction involving an iodoaldehyde and a THF solution of diiodosamarium [26].

2.4
Nitriles

Diiodosamarium in THF induces a reductive coupling of acid chlorides to form α-ketols **6** (Scheme 5) [27]. A mixed coupling between an acid chloride and a ketone may also give ketols **13**. We found that the by-product **14** was produced in many cases by the classical acylation of THF which involves a ring opening catalyzed by a Lewis acid [here the Sm(III) species]. Ruder discovered that SmI_2
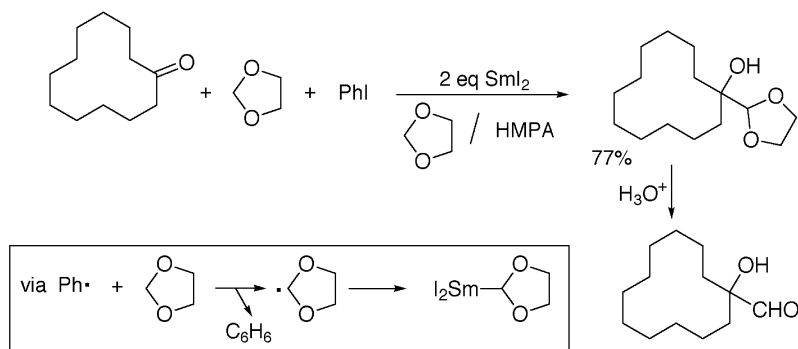
Scheme 4
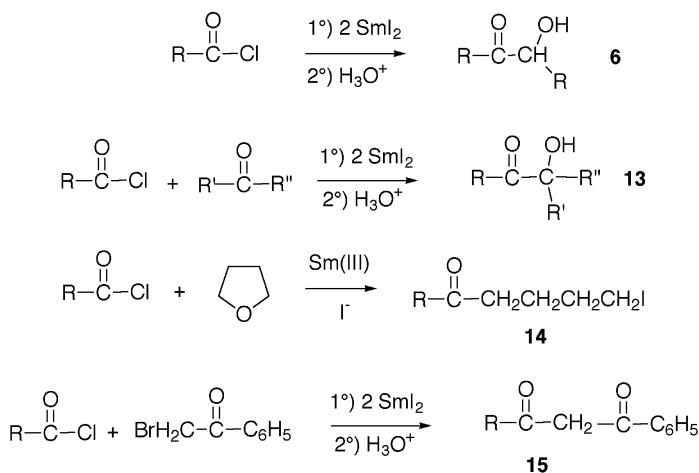
Scheme 5

could be readily prepared in acetonitrile [28]. This author claimed that mixed α-ketols **13** were produced by a two-step procedure and in good yields in acetonitrile. We reinvestigated this work and found that it gave a mixture of products where the pinacol derived from the ketone was the major product [29]. Reactivity of SmI$_2$ in acetonitrile towards acid chlorides is roughly the same as in THF. Many by-products are formed involving some reactions with acetonitrile. In order to avoid the C-H acidity in the α of the nitrile group we investigated the use of pivalonitrile. It is possible to prepare SmI$_2$ (as a slurry) in pivalonitrile from samarium powder and 1,2-diiodoethane [29]. An X-ray crystal structure of SmI$_2$-(NCCMe$_3$)$_2$ was performed by Sen et al. and shows a distorted octahedron around samarium with a bent Sm-N=C structure [30]. The cross-coupling between acid chlorides and ketones gave α-ketols **2** in moderate yields. Barbier reactions are slower in acetonitrile than in THF; however, the regioselectivity of the reactions between allylic halides and ketones is significantly improved (in favor of the unbranched isomer). Surprisingly, HMPA does not enhance the reactivity of SmI$_2$ in nitriles (Barbier reactions or pinacolization of ketones). Reactions are accelerated by catalytic amounts of some transition-metal salts (see Sect. 3.3.6). Diiodosamarium may be prepared in propanenitrile or octanenitrile, but these solvents do not offer special advantages over pivalonitrile.

It is worth pointing out that acetonitrile was used as a cosolvent by Inanaga et al. in 1987 [4]. These authors later studied SmI$_2$-promoted aryl radical cyclization with olefins and obtained quite good yields in acetonitrile [31].

SmI$_2$ in acetonitrile has been used for the preparation in good yields of 1,3-diketones **15** [32]. The authors first added the α-halo ketone to the SmI$_2$ solution and subsequently added the desired acid chloride or anhydride. No comparisons were given between reactions run in THF or acetonitrile.
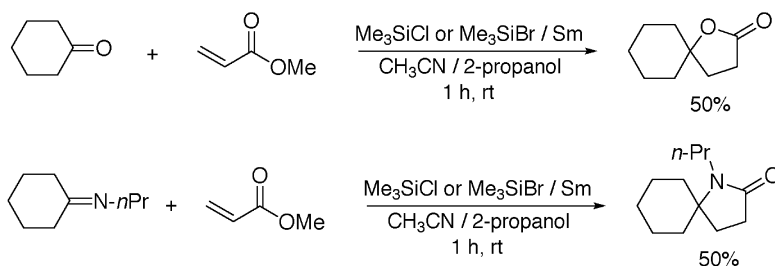
Scheme 6

Ishii et al. prepared an Sm(II) reagent in acetonitrile from NaI, ClSiMe$_3$ and samarium grain. A soluble species was produced with the deep-green color of SmI$_2$ but its structure was not established [33]. At −40 °C this Sm(II) reagent is able to dehalogenate α-chloro or α-bromo ketones or esters, if methanol is present as the proton source. Acetonitrile was superior to THF or DME for this reaction. The reagent gave a faster reaction compared to SmI$_2$/THF for the formation of pinacols of acetophenone [34]. Curiously, benzaldehyde did not produce hydrobenzoin unless HMPA was added. A lactone formation was the result of the coupling of methyl acrylate and a ketone or imine (Scheme 6). Reformatsky-type reactions between ethyl α-bromoacetate and ketones gave satisfactory yields of β-hydroxy esters, without showing any special improvement with respect to the SmI$_2$/THF system. However, it is interesting to note that some Reformatsky or Barbier reactions have been achieved in good yields with octanal, without perturbation by pinacol formation.

2.5
Benzene

It is not possible to prepare SmI$_2$ in benzene from samarium and 1,2-diiodoethane or iodine. However, it was discovered that addition of 10% HMPA as a cosolvent to benzene promoted the reaction of samarium and 1,2-diiodoethane [35]. The reagent reduced various 1,1-dibromoalkenes to the corresponding rearranged alkynes, presumably through the generation of alkylidenecarbenes (Scheme 7). The use of benzene instead of THF avoided the formation of reduced products obtained by hydrogen abstraction. This process was extended to the synthesis of cyclopentenes by C-H insertion on the intermediate carbene [36]. The reaction works especially well from 1,1-diiodoalkanes (Scheme 7). The same authors also used the benzene/HMPA solvent to achieve some SmI$_2$-induced Wittig rearrangements via 1,5-hydrogen transfer of vinyl radicals [37] (Scheme 7). Here again, it is crucial to avoid THF which will induce a competitive intermolecular hydrogen abstraction.
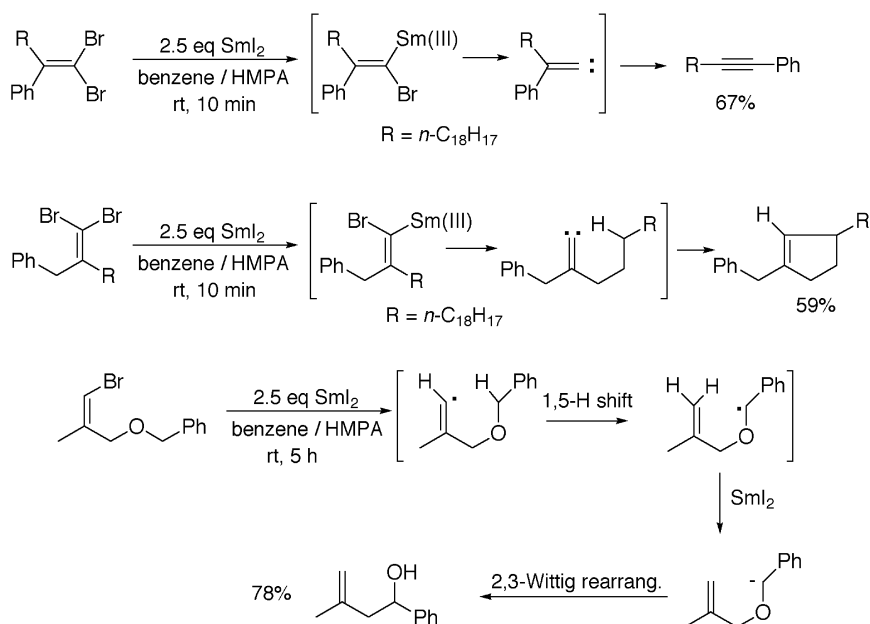
Scheme 7

3
Influence of Additives

3.1
Electron-Rich Additives

3.1.1
Hexamethylphosphoramide (HMPA)

The highly promoted effect of HMPA on reactions of SmI_2 was reported for the first time in 1986 by Inanaga et al. [38] for the reductive cross-coupling of carbonyl compounds with α,β-unsaturated esters (Scheme 8). HMPA was used as a cosolvent with THF (ca. 5%). Enhancement of the coupling rates and yields were quite remarkable; however, the diastereoselectivity was sometimes diminished in the presence of HMPA.

Independently, Fukuzawa and co-workers [39] reported intramolecular reactions leading to bicyclic γ-lactones from keto or aldo α,β-unsaturated esters (Scheme 9). The reaction was mediated by SmI_2 in the presence of HMPA (THF/HMPA=10/1) but the beneficial effect of HMPA was less obvious in that case.

Scheme 8

none: 4 h; 65°C; yield = 56%; **16/17** = 64/36

HMPA: 1 h; 65°C; yield = 47%; **16/17** = 79/21
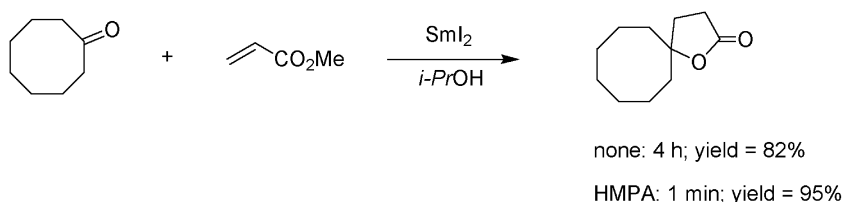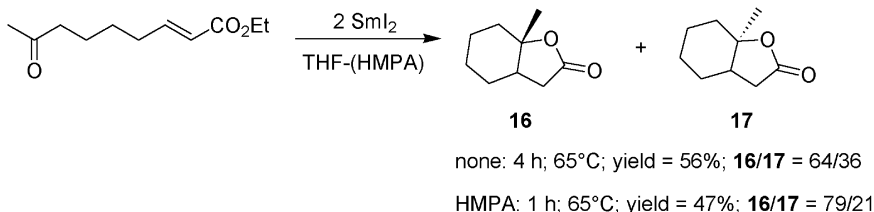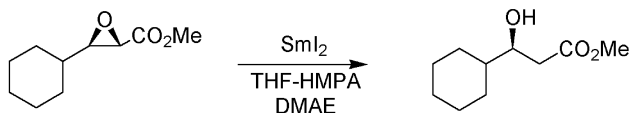
Scheme 9

Scheme 10

Inanaga et al. have developed the use of HMPA for the highly regioselective reduction of α,β-epoxy esters and δ,γ-epoxy α,β-unsaturated esters [40] (Scheme 10).

The best results were obtained when HMPA (5 equiv) and dimethylamino ethanol (DMAE, 2 equiv) were used as additives. The authors also reported the reductive cross-coupling of 1,3-dioxolane with carbonyl compounds to yield α-hydroxy derivatives [24]; the reaction was performed in the presence of HMPA (ca. 5% of the solvent) and was complete within 5 min at room temperature (Scheme 11).

A remarkable effect by HMPA was observed in the reduction of organic halides with SmI_2 in THF [41] (Scheme 12).

As mentioned in Sect. 2.3, Inanaga and co-workers have demonstrated that Barbier-type reactions of organic halides with carbonyl compounds are promoted by addition of HMPA [16]. They reported a mild convenient method for the direct synthesis of lactones from bromo esters and ketones or aldehydes by using a HMPA-promoted Barbier-type reaction with SmI_2 (Scheme 13). They also found that the SmI_2/THF-HMPA system was highly useful for the generation of

Scheme 11

Scheme 12

none: 2 h; rt; yield = 39%

HMPA: 1 min; rt; yield = 85%
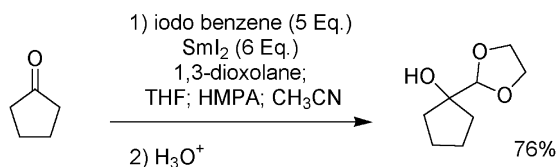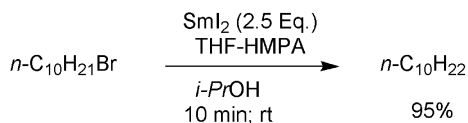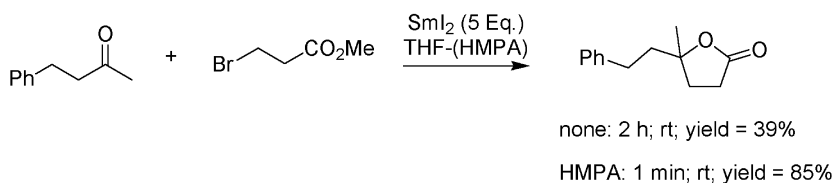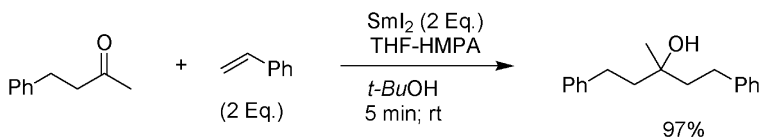
Scheme 13

Scheme 14

ketyls and their intramolecular addition to a variety of activated olefins [42] (Scheme 14). In addition, this system has been used to successfully reduce organo heteroatom oxides including triphenyl phosphine oxide [43].

Thus the most popular way to increase the rate of reactions of diiodosamarium has become the use of a mixture of THF–HMPA (90–95:10–5) as solvent. Although the coordination of HMPA to the Sm(II) ion was thought to be responsible for this effect, the role played by HMPA remained unclear until 1994.

In order to clarify this problem, Hou and Wakatsuki [44] prepared SmI_2/HMPA complexes by addition of HMPA to a blue solution of SmI_2 in THF. The resulting

0.250 nm

HMPA,,,|,,,\HMPA
HMPA/ | \HMPA

0.339 nm
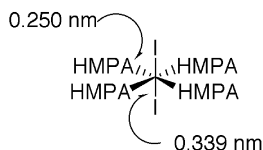
Scheme 15

purple solution was concentrated and toluene was added. After a few days at room temperature, black-purple blocks of $SmI_2(HMPA)_4$ were deposited in 90% yield, and they were structurally characterized. It appears that the Sm(II) ion sits on an inversion center and is bonded by two I^- anions and four HMPA ligands in a distorted octahedron. The central Sm(II) ion and the four HMPA ligands are exactly coplanar and the two iodide anions are mutually trans (Scheme 15).

In a recent work, electrochemical studies of the reducing power of SmI_2 in THF and the effect of HMPA cosolvent as a function of concentration have been reported [45]. This effect was studied by recording a linear sweep voltamogram for each cosolvent addition. The oxidation potential vs. the $Ag/AgNO_3$ reference electrode for 0 to 6 equiv of HMPA cosolvent was measured. The addition of 3 equiv of HMPA to SmI_2 had a drastic effect on the redox potential, increasing the oxidation potential from –1.33 to –1.95 V. The addition of 4 equiv of HMPA to SmI_2 increased the potential even further to –2.05. Further addition of HMPA showed no effect on the redox potential.

These observations are consistent with the structure determined by Hou et al.; the complex $SmI_2(HMPA)_4$ should be the reactive intermediate responsible for the unique reactivity of the SmI_2/THF–HMPA system.

Preparation, structural characterization and reactivity studies of SmI_3–HMPA complexes have also been performed [46]. The composition of the dried complex was found to be $SmI_3(HMPA)_4$. The reactivity of this complex was examined in comparison with that of SmI_3 in THF only. In contrast to the latter complex, the HMPA complex was not reduced to low-valent samarium species by *n*-butyl lithium or *sec*-butyl lithium. These results might be interpreted by considering that this Sm(III) complex is well stabilized by the coordination of HMPA which could be one of the driving forces for the facile electron transfer from SmI_2–HMPA complexes.

Molander et al. [47] suggested that other factors could be involved in the effective role of this additive: disaggregation of SmI_2, f-orbital perturbation due to the ligand field effect in the presence of the strong donor ligand HMPA raising the energy of the HOMO (electron-donating orbital). A combination of these effects might also be considered.

The effect of HMPA on the spectroscopic properties of SmI_2 has also been examined [48].

We wish to review here some studies that stress the specific role played by HMPA in samarium diiodide reactions.

Reduction of 1-iodo-5-hexene with SmI$_2$/THF–HMPA has been studied by Curran and co-workers [49] (Scheme 16). They found that reaction is slow without HMPA. A reasonable reaction time (<10 min) is attained with 2 equiv of HMPA per SmI$_2$. In the range from 1.3 to 4.4 equiv, the ratio of directly reduced product to the rearranged product increases dramatically (from 8:92 to 54:46). Increasing the amount of HMPA beyond 5 equiv results in a very slow decrease in the ratio. These results are consistent with the above results concerning the structure of the complex SmI$_2$–HMPA [44] and the electrochemical studies [45]. The easier the reduction of the 5-hexenyl radical to organosamarium species, the less the cyclopentyl-carbinyl radical is formed.

Curran et al. demonstrated that reduction of aryl halides to radicals is also strongly accelerated in the presence of HMPA, as well as reduction of alkyl radicals to alkyl samarium [50,51] (Scheme 17).

HMPA is also necessary for the in situ preparation of the organosamarium species from alkyl halides and SmI$_2$ in THF [52]. A similar effect was also observed in the case of reactions performed in tetrahydropyran [23].

Molander et al. studied the intramolecular coupling of unactivated olefinic ketones by a reductive ketyl-olefin radical cyclization, mediated by SmI$_2$ in the presence of HMPA [47] (Scheme 18).

HMPA was required to promote efficient ketyl-olefin cyclization in the desired manner. It seems that factors other than reduction potentials also play a
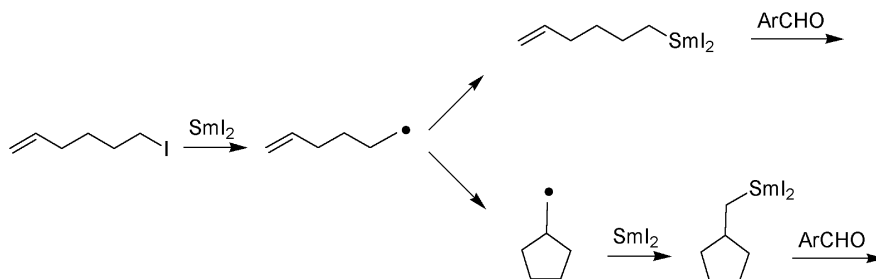
Scheme 16
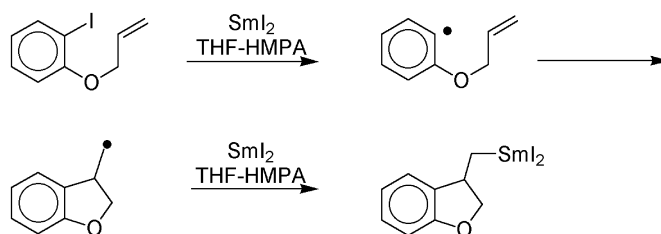
Scheme 17

role in the efficiency of HMPA as an additive in SmI$_2$-promoted reactions: ketyl radical anions appear to have greater persistence when generated in the presence of HMPA than without additives. By progressively increasing the amount of HMPA, from 0 to 8 equiv, the percentage of **20** (generated by hydrogen abstraction from the solvent) decreased and the stereoselectivity of **19** increased. These enhanced diastereoselectivities were attributed to an added steric component in the cyclization transition states. As an application, SmI$_2$ in the presence of HMPA has been used to promote 8-*endo* cyclization of various keto olefins affording a variety of eight-membered ring products in fair to excellent yields [53]. This success was in part attributed to the formation of ketyls exhibiting remarkable persistence in the presence of HMPA perhaps because the HMPA excludes the proton source (*t*-BuOH) from the coordination sphere of the Sm(III) ion.

The successful intramolecular coupling between vinyl oxiranes and ketones mediated by SmI$_2$ in the presence of HMPA as a cosolvent has been reported [54] (Scheme 19). The use of HMPA as a cosolvent allowed the couplings to be performed at lower temperatures and improved the regioselectivity of the process as the 1,5-diols were then the only products isolated; the *E/Z* ratio was also affected.

5 or 6 membered ring
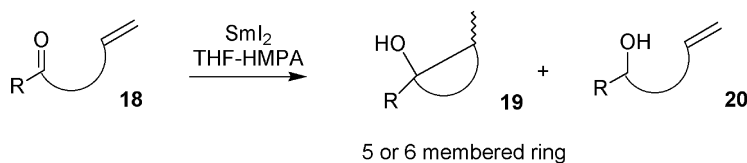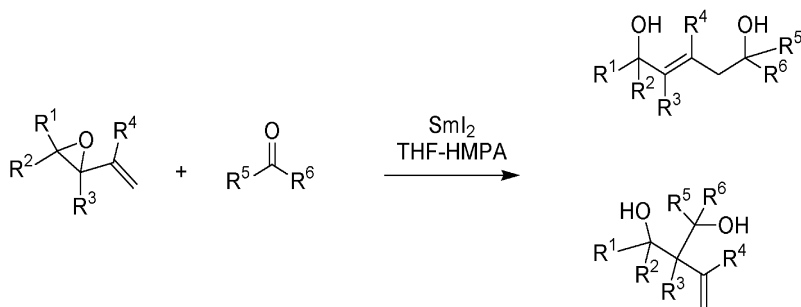
Scheme 18

Scheme 19

Studies by Molander et al. have demonstrated that samarium diiodide efficiently promotes the intramolecular coupling of ketones with distal epoxy olefins in the presence of HMPA, in good yields and often with high diastereoselectivity (Scheme 20). When tetramethylguanidine was used instead of HMPA, the desired carbocycle was obtained in good yield but the diastereoselectivity was diminished [55]. Evidence has been presented that suggests that the reaction proceeds via an initial radical cyclization route although reaction via an allyl samarium species cannot be ruled out.

In order to achieve the total synthesis of (–)-anastrephin, a *D*-glucose-derived α,β-unsaturated ester, was subjected to an SmI$_2$-mediated intramolecular reductive coupling reaction with the SmI$_2$/THF–HMPA system. The reaction proceeded with moderate stereoselectivity leading to a diastereomeric mixture of hexahydro benzofuran-2(*3H*)-ones in which a *cis*-fused product was the major isomer [56] (Scheme 21). The presence of HMPA was essential for smooth coupling; significant reduction of the aldehyde to a hydroxymethyl group occurred without HMPA.

The use of HMPA can modify the course of a reaction. It is well known that aromatic aldehydes or aromatic ketones readily couple to pinacols **21** on treatment with SmI$_2$ in THF, but addition of 2.8 equiv of HMPA leads to the formation of product **22** that results from connecting a *para* carbon with the carbonyl of another molecule (Scheme 22).

It is proposed that HMPA molecules coordinate with samarium ions through their oxygen atom because the ketyls and ortho carbons are hindered by the HMPA ligands; coupling at the *para* position with a second molecule of benzaldehyde would be favored [57,58].

Scheme 20

(3a *S*; 7a *R*)
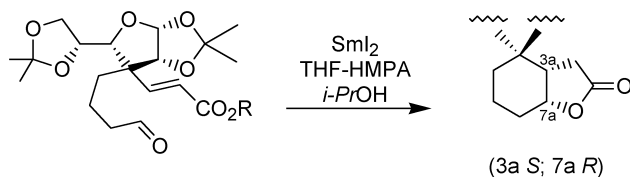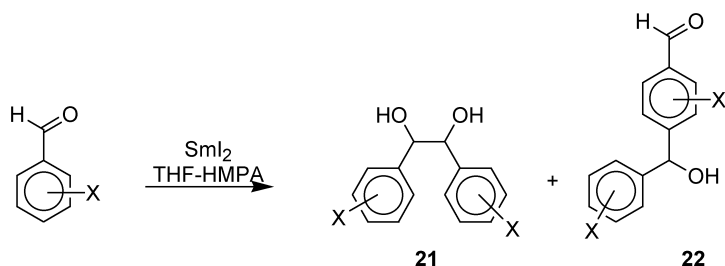
Scheme 21

Scheme 22
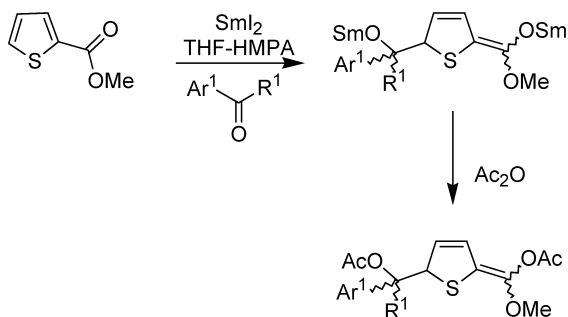
Scheme 23
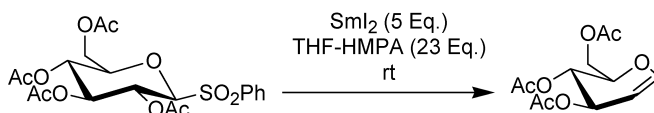
Scheme 24

Similarly, methyl thiophenecarboxylate reacts at the C5 position with a series of substituted benzaldehydes and acetophenone in the presence of the SmI_2/THF–HMPA system to give a samarium enediolate which can be trapped by a second electrophile [59] (Scheme 23). The samarium-bonded ketyl anion radical does not trap the hydrogen atom or undergo acyloin coupling, presumably due to the hindrance of the ligated HMPA molecules.

Very interesting chemistry has been developed with sulfones and samarium diiodide.

Neither deoxygenation nor desulfonylation occurs upon treatment of various phenylsulfones with SmI_2/THF. However, in the presence of HMPA, reductive desulfonylation was achieved [60]. Thus a series of substituted glycosyl phenyl-sulfones was converted into the corresponding glycals with SmI_2/THF–HMPA [61] (Scheme 24).
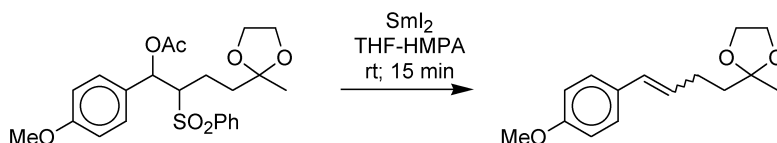
Scheme 25
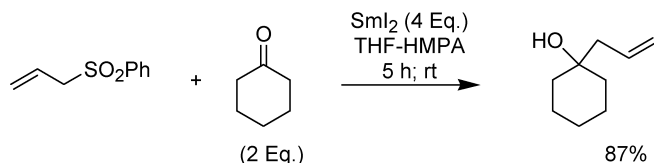
Scheme 26
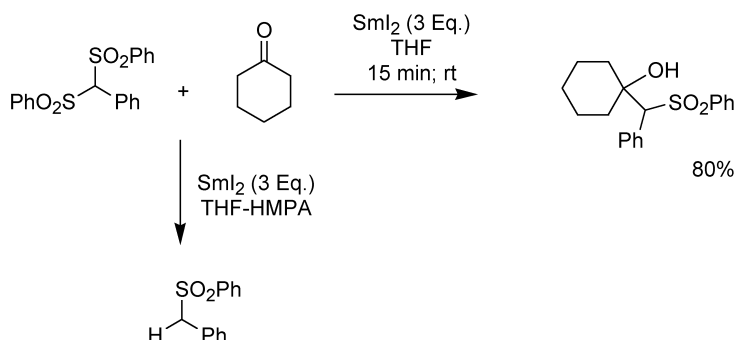
Scheme 27

The Julia alkylidenation was improved using SmI_2/THF-HMPA instead of Na(Hg) for the reductive elimination step. In contrast, a poor result was reported without HMPA [62] (Scheme 25).

In the presence of HMPA, allylic sulfones react with SmI_2 and ketones to give a Barbier-type reaction (Scheme 26). Much lower yields are obtained if the reagents are not thoroughly degassed, and in the absence of HMPA [63].

Completely stereoselective cyclizations using formyl allyl sulfides and sulfones have been described. Optimum conditions involved the slow addition of a solution of the starting material in THF to a 0.1 M solution of SmI_2 containing 8 equiv of HMPA in THF at −10 and −78 °C, respectively [64].

It has also been reported that SmI_2 mediates the in situ reductive addition of geminal bis-phenyl sulfones to ketones in THF. In the presence of HMPA (10 equiv), addition to the carbonyl is completely suppressed, but not desulfonylation [65] (Scheme 27).

Reaction of β-hydroxy or β-acetoxy sulfones with SmI_2 in the presence of HMPA caused effective reductive elimination to provide olefins [66]. In contrast, Kende recorded a poor result in the reductive elimination of the β-hydroxy phenyl sulfones with SmI_2 without HMPA [67]. Finally, it has been reported that contrary to phenyl sulfones, 2-pyridyl sulfones are instantaneously reduced in the presence of SmI_2 without additives [68].

Samarium(II) triflate, a promising reagent for selective organic synthesis, has been prepared by treatment of a THF solution of $Sm(OTf)_3$ with 1 equiv of an organolithium (or organomagnesium) reagent at room tempeature [69,70] (Scheme 28). Generation of the samarium(II) was unsuccessful in the presence of HMPA.

The $Sm(OTf)_3$ reagent mediates the Grignard-type reaction in THF–HMPA. Alkylation, allylation and benzylation of ketones and aldehydes with alkyl, allyl or benzyl halides proceeded via stable organosamarium intermediates [69] (Scheme 29).

Matsuda et al. have studied the hydroxyl group directed intermolecular ketone-olefin coupling reactions, induced by SmI_2, between α-hydroxy ketones and α,β-unsaturated esters or nitriles (Scheme 30). It was noted that reactions

Scheme 28

Scheme 29

none: 0°C; yield = 91%; ds = 90/10

HMPA: 0°C; yield = 95%; ds = 79/21
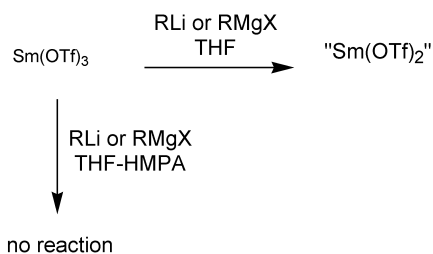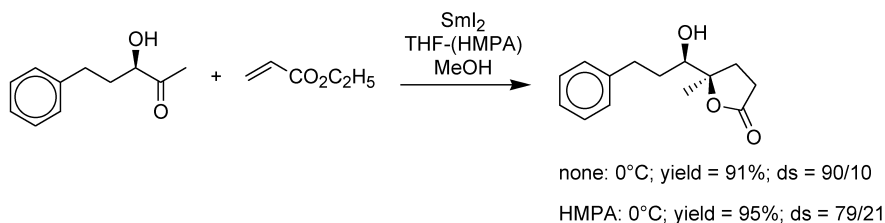
Scheme 30

run in the presence of HMPA resulted in all cases in some depression in the diastereoselection [71–73]. Various other reactions have been reported which exemplify the crucial role of the solvent HMPA.

Inanaga et al. achieved the hydrodimerization of conjugated esters and amides with the SmI_2/THF–HMPA system in the presence of a proton source [74].(Scheme 31). However, inexplicably, Alper et al. achieved reductions (not reductive dimerization) of the double bond of α,β-unsaturated esters and amides with the same system [75]. In the latter paper, however, the presence of a proton donor is not mentioned.

The reductive coupling of α-bromoacetate to succinic acid diesters mediated by SmI_2 in the presence of HMPA has been reported [76] (Scheme 32).

In contrast, reactions performed without HMPA as additive do not lead to dimerization but to β-keto esters [77] (Scheme 33). Obviously, the intermediate samarium enolate which is formed behaves in a different way according to the presence or the absence of HMPA.

The reductive dimerization of cyclopropane-1,1-dicarboxylic esters using SmI_2/THF has also been reported (Scheme 34). In this case, the addition of
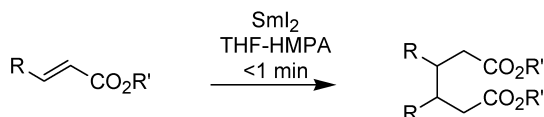
Scheme 31
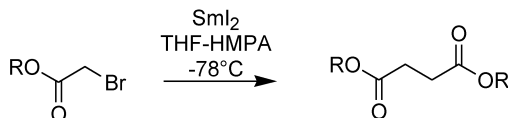
Scheme 32
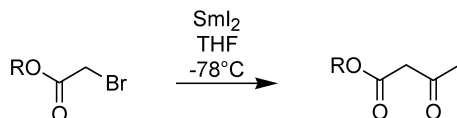
Scheme 33
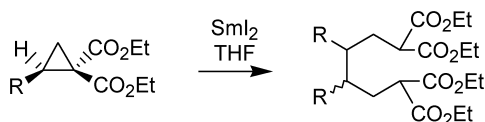
Scheme 34

HMPA did not improve yields of the dimer. On the contrary, yields were higher in the absence of HMPA [78].

A new intramolecular reductive carbon–carbon bond formation has been noted in reactions of 1-(2-formyloxyethyl)-3-formyl-oxycycloalkene with SmI$_2$ giving a spiro hemiacetal (Scheme 35). The absence of HMPA caused a considerable decrease in the yield of the hemiacetal [79].

Coupling reactions of indoles and carbonyl compounds (either intra- or intermolecularly) have been described. This is a new method for hydroxylation at the C2 position of indole (Scheme 36). The role of HMPA is crucial to prevent reduction or pinacolic coupling of aromatic carbonyl compounds [80].

Stereocontrolled decalin ring annulation reactions through the hydroxyl group directed pinacol coupling using SmI$_2$ have been reported by Matsuda and et al. Stereocomplementarity was observed depending on the presence or absence of HMPA [81] (Scheme 37). The authors propose that without HMPA only the aldehyde of the substrate is reduced to the ketyl radical during the initial re-
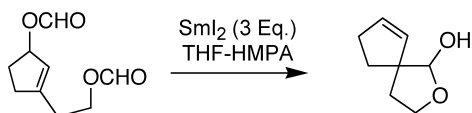
Scheme 35
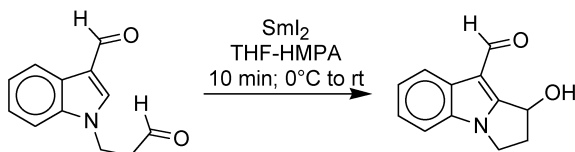
Scheme 36
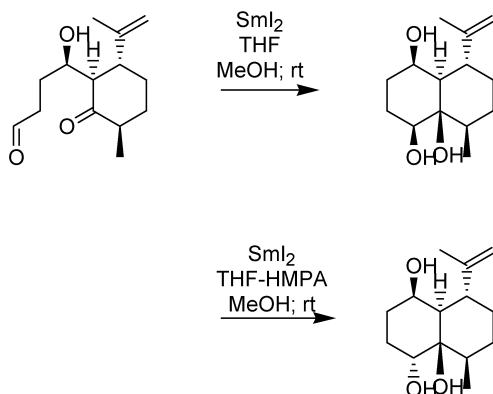
Scheme 37

duction by SmI$_2$, whereas in the presence of HMPA a ketyl radical pair is generated through a single electron transfer from SmI$_2$.

Katritzky et al. have prepared α-amino carbanions from tosyl methyl amines. The transformation was achieved by treatment with 2 equiv of SmI$_2$ [82] in the presence of an electrophile (Scheme 38). In the absence of HMPA the use of iso-butyraldehyde as the electrophile gave only the amine dimer (98%). However, the addition of 5% of HMPA resulted in a 67% yield of the desired product (62%) with a minor amount of diamine (17%). The formation of the hydroxy amine probably involves a carbanion intermediate whereas coupling gives the diamine.

Samarium diiodide has also been used for the intramolecular coupling of aldehydes and ketones with *O*-benzyl formaldoxime [83], for the corresponding intermolecular coupling with diphenylhydrazone [84,85] and for the intramolecular coupling of an α,β-unsaturated ester with an oxime ether [86] (Scheme 39). In all these cases the addition of HMPA was found to be essential for a successful reaction.

3.1.2
N,N'-Dimethylpropyleneurea (DMPU)

Because of the toxicity of HMPA, studies on other samarium(II) additives have been carried out by several researchers. DMPU, a well-known and less toxic alternative to HMPA, has sometimes been used as a cosolvent for SmI$_2$ reactions. Addition of DMPU to a THF solution of SmI$_2$ results in an immediate color change from blue to purple.
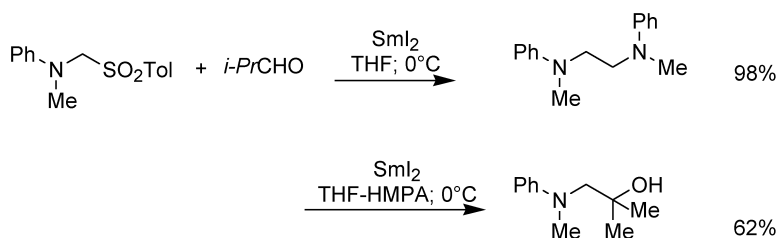
Scheme 38
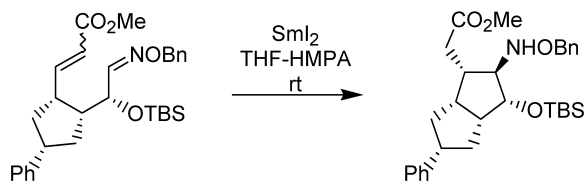
Scheme 39

Curran et al. were the first to use SmI$_2$/THF–DMPU. This system promoted a tandem radical cyclization [87] (Scheme 40). Reduction of **23** with SmI$_2$/THF produced **24**, **25** and **26** in low yield; addition of HMPA accelerated the reaction and gave **24** in 91% yield. DMPU as additive gave similar results to HMPA with respect to reaction rate and yield but **25** and **26** were also formed albeit in low yield (9 and 4%). In addition, the cyclization in THF–HMPA required less than 2 equiv of SmI$_2$ (1.3 equiv) but when DMPU was used, a larger excess of SmI$_2$ was needed, perhaps because the reaction mixture was heterogeneous.

Ring scission of cyclic β-halogeno ethers to olefinic alcohols mediated by SmI$_2$ has been studied. Scission in the tetrahydrofuran series could be accelerated by addition of HMPA or DMPU with only a small deterioration in diastereoselectivity, but in the tetrahydropyran series there was a drastic change in the stereochemistry of the product when DMPU was used. Obviously, DMPU has a substantial effect on the formation and conformation of complexes in solution [88,89].

A mixture of THF and DMPU has been used as a solvent for SmI$_2$ in various reactions such as cyclization of alkynyl halides [90,91], tandem iodo-enone cyclization/samarium enolate aldol reaction [92], coupling of β-silylacrylic esters [93], deprotection of arenesulfonamides [94] and pyridine-2-sulfonamides [95], radical ring-opening reactions of cyclopropyl ketones and the trapping of the resulting samarium(III) enolates by a variety of electrophiles [96] (Scheme 41).

From the above studies, the SmI$_2$/THF–DMPU combination emerges as the most useful, in particular because in this case the problem of second electron delivery is avoided.
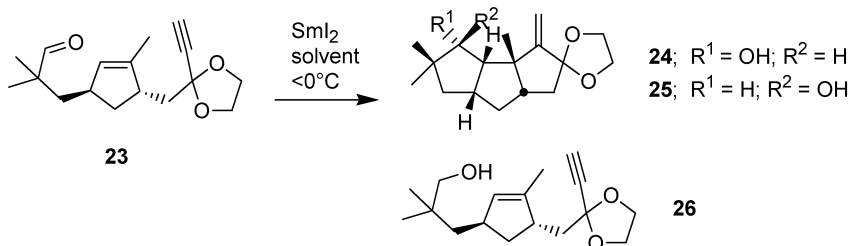
Scheme 40
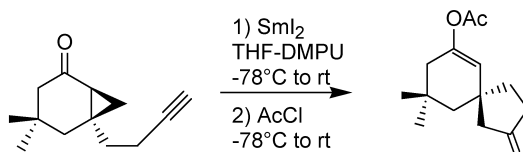
Scheme 41
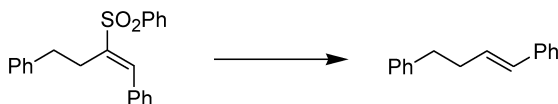
Scheme 42

The SmI$_2$/THF–DMPU system has also been used as an alternative to the Na(Hg) amalgam in the Julia–Lythgoe olefination [97] (Scheme 42). It was found that this system gave a positive rate enhancement (from 95% in 5 d with SmI$_2$/THF to 95% in 35 min). The DMPU reaction also gave considerably higher stereoselectivity (E/Z=9:1) than was observed using HMPA. Further studies to optimize the reactions have led to the use of 10 to 20 equiv each of DMPU and MeOH, respectively, which gives reasonable reaction times (35 min) and high selectivity for the E olefin (99:1).

The role of DMPU has been studied by Curran et al. in the reduction of an o-(allyloxy) iodobenzene. It was found that DMPU is much more efficient in MeCN than in THF [98]. The reduced effectiveness of DMPU in THF may be due in part to formation of an insoluble SmI$_2$/DMPU complex.

3.1.3
Other Nitrogen Ligands

Various other commercially available nitrogen ligands have been screened to increase the reducing power of SmI$_2$ in THF.

Inanaga et al. have studied the selective conjugate reduction of α,β-unsaturated esters and amides with SmI$_2$. While the reductive dimerization was promoted by HMPA [74], the use of dimethylformamide (DMF), dimethylacetamide (DMA), tetramethylurea (TMU) and bidentate ligands such as N,N,N',N'-tetramethylethylenediamine (TMEDA)and $N,N,N'N'$-tetramethylpropylenediamine (TMPDA) were effective for the conjugate reduction of the substrate. DMA was found to be the most promising. In contrast, in the presence of the tridentate chelating agent $N,N,N'N''N''$-pentamethyldiethylenetriamine, no reaction took place. This result might be due to the complete occupancy of the coordination sphere of samarium [99].

The formation of an aryl radical from the corresponding aryl iodide or aryl bromide using SmI$_2$ has been carried out in the presence of various other nitrogen ligands (Scheme 43). The results obtained with Et$_3$N, DBU or TMG were satisfactory or even superior to the ones obtained with HMPA (**27+28**: 71%; 4 h; **27/28**=81:29). It is worth noting that the ligand/SmI$_2$ molar ratio has practically no effect on the reaction course if more than 2 equiv of ligand are present [100].

TMEDA has sometimes been used as an additive in the reduction of α,β-epoxy esters. In this case it was associated with HMPA and isopropanol [40], as,
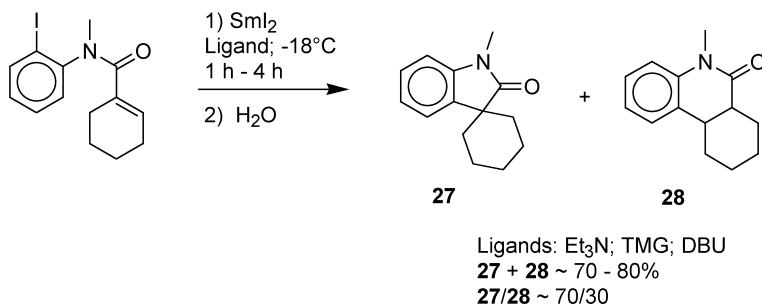
Scheme 43

Scheme 44
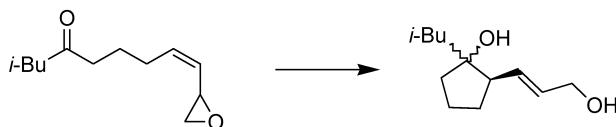
Scheme 45

for example, in the intermolecular aldol-type reactions of phenacyl bromides with carbonyl compounds [101] and for the reduction of cyclopropyl lactones [102] (Scheme 44).

TMG has been used for the cyclization of a keto vinyl epoxide (Scheme 45). Better yields were achieved than with HMPA; unfortunately, a 1:1 mixture of diastereomers was obtained [55].

The effect of cosolvents (TMP, DBU, PMP, TMU, NMP, DMPU) on the oxidation potential of SmI_2 in THF has been studied. The change in the reducing power of SmI_2 is dependent on the nature and concentration of these cosolvents. For example, the SmI_2/TMU reducing species was determined to have an E_{ox} of $-1.99\,V$ (vs. an $Ag/AgNO_3$ electrode) at 30 equiv of cosolvent while the SmI_2/DMPU complex displayed an E_{ox} of $-2.21\,V$ at the same cosolvent concentration. The effect of water on the E_{ox} of SmI_2 was also determined; it was found that 55 equiv of water increased the oxidation potential to $-1.74\,V$ [103].

3.1.4
Miscellaneous

Kamochi and Kudo found that the reducing ability of SmI_2 is enhanced by addition of a base (KOH, $LiNH_2$ or LiOMe), allowing the fast reduction of carboxylic acids to alcohols [104]. Reduction of nitriles to primary amines has also been realized by the system SmI_2/50% KOH (1:2) in a few minutes at room temperature [105].

BINAPO (the bis-oxide of BINAP) can complex samarium and gives some stereocontrol in the formation of γ-butyrolactones by reaction of ketones with α,β-unsaturated esters and SmI_2 in THF. Enantiomeric excesses (ee's) of up to 90% were obtained [106].

3.2
Proton Sources

All the reactions induced by SmI_2 start with a one-electron transfer giving rise to an anion radical which evolves in various ways: radical chemistry, cleavage into a carbanion and a radical, further reduction to a dianion, etc. Very often marked differences in the product distribution are observed when SmI_2-induced transformations are performed in aprotic or protic conditions, because in the latter case in situ protonation of key intermediates may occur. Kinetic stability of SmI_2/THF solutions in the presence of some water or alcohols have been reported [15,107]. It is then possible to use these solutions for in situ protonation of end products or intermediates. For example, it has been firmly established that the samarium Barbier reaction between an organic halide RI and a ketone involves a reactive organosamarium intermediate $RSmI_2$ since the reaction performed in the presence of SmI_2/THF–t-BuOD or EtOD leads to the formation of some RD. Under the same conditions, and in the absence of ketones, the deuteration of RI into RD was also achieved in good yield [108,109].

Apart from its usefulness for some mechanistic investigations the presence of protic additives may disturb the course of a reaction and change the product distribution. It is this aspect which will be considered here.

3.2.1
Water

In 1980, we established that water was the additive of choice for the SmI_2 reduction of ketones and aldehydes [15]. In fact, there is growing evidence that water serves not only as a proton source but can also accelerate certain classes of samarium reductions. Addition of water to THF solutions of SmI_2 induces a color change from the original deep blue to a wine-red similar to the one encountered in a THF–HMPA mixture. The color persists for a few hours if pure and thoroughly deaerated water is used. It appears that water acting as a coordinating ligand (as well as a proton source) greatly increases the reducing ability of SmI_2

(see Sect. 3.1.3 and [103]) and THF–H_2O can thus be considered to be in some reactions a good substitute for THF–HMPA.

Curran et al. have studied reductions of 1,3-diphenylpropanone, ethyl cinnamate, diphenyl sulfoxide, 1-iododecane, and *o*-allyloxyiodobenzene with SmI_2 in the presence of water [98] (Scheme 46). The accelerating role of water in the reduction of alkyl and aryl iodide has been readily demonstrated [99].

Inanaga et al. reported the use of a 37% aqueous solution of formaldehyde for the reductive cross-coupling of carbonyl compounds with α,β-unsaturated esters with the SmI_2/THF–H_2O system [38] (Scheme 47).

Ohgo et al. have achieved a cross-coupling reaction of aldehydes with α-diketones to give the corresponding adducts [110] (Scheme 48); reactions without HMPA gave better results compared with the reactions using HMPA as additive.

Scheme 46

Scheme 47

Scheme 48

Unprotected tetrono- and pentonolactone undergo an α-deoxygenation reaction mediated by SmI_2 in $THF-H_2O$ [111] (Scheme 49). The NO reductive cleavage reaction is also accelerated by addition of water [86].

Kamochi and Kudo have reported the use of the $SmI_2/THF-H_2O$ system to reduce aromatic carboxylic acids to alcohols (Scheme 50). Furthermore, aromatic esters amides and nitriles were similarly reduced by this system in good yield [104]. As indicated above, reduction of carboxylic acids to primary alcohols is also effective with SmI_2 in a $THF-H_2O-NaOH$ mixture [105]. In contrast, without water these substrates remain unchanged. With the $SmI_2/THF-H_2O$ system, pyridine was rapidly reduced to piperidine; in similar reactions with pyridine derivatives bearing chloro, amino and cyano substituents, these functionalities were partly eliminated to afford pyridine or piperidine [107].

Curran and Studer transformed in good yields some aromatic dimethylacetals to methylbenzylacetals, by an overall process of reductive demethoxylation [112]. This reaction works by addition of 4 equiv of H_2O at room temperature.

The reduction of allylic halides (in the cepham family) by SmI_2/THF in the presence of some water gave a very fast transformation into exomethylene cephams [113]. The authors made the hypothesis that an intramolecular protonation occurs in a σ-allylsamarium by H_2O coordinated to samarium.

3.2.2
Alcohols

3.2.2.1
Reduction of Carbonyl and C=N Groups

We have shown that THF–MeOH solutions of SmI_2 are excellent reducing agents of ketones or aldehydes to the corresponding alcohols [15]. A mechanistic study
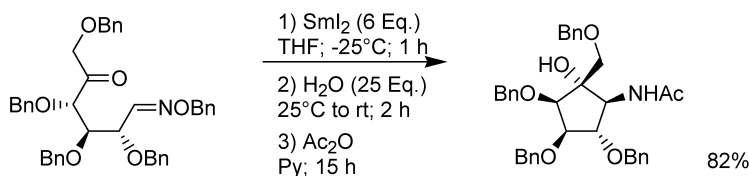
Scheme 49
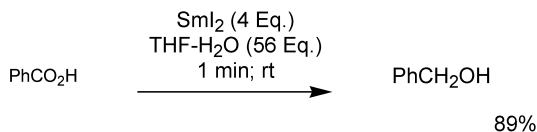
Scheme 50

with MeOD established that 2-octanone was transformed into 2-D-octanol, presumably through the intermediate formation of the carbanion obtained by the reduction of the hydroxy radical issued from the ketyl protonation [114]. Reduction of a mixture of aldehyde and ketone gave a high preference for the aldehyde reduction [15].

The combination of SmI_2 and trimethylsilyl chloride (in replacement of *t*-BuOH) in THF–HMPA was found to accelerate the reduction of sterically hindered or enolizable ketones such as 6-keto- or 20-keto-steroids and 5-cholestenone [115].

Isocyanates R–N=C=S have been transformed by SmI_2 in good yields into thioformamides RNH–(H)C=S in THF–HMPA in the presence of *t*-BuOH at –78 °C [116]. The use of *t*-BuOD gave the C-deuterated thioformamide, establishing that the reaction occurs by two successive one-electron transfers giving this carbanion which is trapped by in situ protonation.

3.2.2.2
Pinacol Formation

In 1983 we recognized that aprotic THF solutions of SmI_2 gave pinacol formation from aldehydes or ketones; the reaction being quite fast with aldehydes or aromatic ketones [117]. However, aromatic carbonyl compounds were coupled in THF by the samarium/I_2/MeOH system, SmI_2 being formed in situ [118].

Hanessian et al. discovered that the intramolecular reductive coupling of various 1,6- and 1,5-dialdehydes gave mainly *cis*-diols [119]. This useful methodology involves the presence of an alcohol (*t*-BuOH or MeOH) acting as an in situ protonating agent for the reaction intermediate. For example, the *myo*-inositol derivative **29** [120] and **30,** an intermediate in the total synthesis of forskolin [121], have been synthesized (Scheme 51). An intramolecular coupling of α-keto aldehyde was also successful, giving a bicyclic system **31** which may be a relay in the total synthesis of taxoids [122].

3.2.2.3
Carbonyl-Ene Couplings

The reductive coupling of ketones or aldehydes with electrophilic alkenes such as conjugated esters (Scheme 52) has been described independently by Inanaga et al. [38] and Fukuzawa et al. [123,124]. The reaction was performed in THF either in the presence of HMPA [38] or an alcohol [123,124]. The mechanistic aspects of this reaction have been discussed [124]. Presumably, the ketyl radical or its protonated form adds to ethyl acrylate with formation of the C–C bond. An efficient enantioselective synthesis of γ-butyrolactones has been derived by using *N*-methylephedrinyl acrylate or crotonate [125]. One example (synthesis of **33**) is indicated in Scheme 52.

The intramolecular reductive ketone-olefin coupling was realized by Molander et al. by the combination SmI_2/THF–*t*-BuOH [126]. For example, the spiro-

Scheme 51

Scheme 52

cyclic lactone **34** was obtained with high diastereoselectivity because of chelation of oxygens on Sm^{3+} (Scheme 52). The protic conditions prevented a retro-aldol process occurring, as observed under aprotic conditions.

Iminium salt **35** was reduced in anhydrous acetonitrile in the presence of at least 1 equiv of camphorsulfonic acid (CSA) (Scheme 52) [127]. In this way, pyrrolidine **36** was obtained in good yield. The cyclization presumably involves a *N*-protonated unsaturated α-amino radical, while the non-protonated form gives less cyclization and more reduction of the C=N bond.

Triple bonds may also undergo coupling reactions to a carbonyl. Inanaga et al. found that the reduction system SmI_2/THF–HMPA–*t*–BuOH efficiently promotes the carbonyl addition on the triple bond, generating allyl alcohol **37** [128] (Scheme 53). A similar procedure was used for the intramolecular coupling reaction [129]. The highest yields were observed for compounds with electron-withdrawing groups on the terminal site of the alkyne, as for the reactions described in Scheme 53.

Scheme 53

　　Intramolecular reductive coupling of aldehydes and allenic esters has also been described [130]. For example, aldehyde **38** was transformed into cyclopentanols **40a** and **40b** (Scheme 53). Presumably ketyl **39** is an intermediate in the reaction. Although being nucleophilic in character it adds to the carbon adjacent to the ester group because of the chelation on samarium, which explains the good diastereoselectivity. The use of homologous aldehydes of **38** should generate rings of larger size than cyclopentane; however, the cyclizations are difficult and need adjustments to the experimental conditions. A six-membered ring analog of **40** was obtained by using methanol instead of *tert*-butanol. The seven-membered homolog **42** was produced in acetonitrile containing 10 equiv of water. Aldehyde **41** was transformed into different products **43** and **44** by minor changes in the experimental conditions.

3.2.2.4
Cleavage of Carbon–Heteroatom Bonds

α-Heterosubstituted ketones are a very widely represented class of compounds amongst organic compounds. Reduction of α-heterosubstituted ketones to ketones is a useful synthetic operation. In 1986 it was shown that SmI_2 is a good reagent for this transformation, which was achieved under mild conditions (–78 °C) in THF–MeOH [131]. For example, α-substituted ketones **45** (Scheme 54) were reduced in 2-dodecanone in good yield for various X groups. Only X=OH gave a poor yield of the desired ketone. The authors envisioned that the initial step of the reaction is formation of an α-ketyl which is rapidly protonated by methanol. A second electron transfer should produce a carbanion which generates an enol by β-elimination. Finally, the enol tautomerizes into the ketone. Under the above experimental conditions α-acetoxy esters were not reduced, a different result to that with α-bromo esters or α-bromo ketones.

　　The reduction of cyanophosphates **46**, readily prepared from ketones or aldehydes with diethyl phosphorocyanidate and lithium cyanide, led to nitriles in excellent yields [132] (Scheme 54). This reductive cyanation process has also

45　X = OAc, OTMS, OTs　　　　　　　　　　　good yields

46
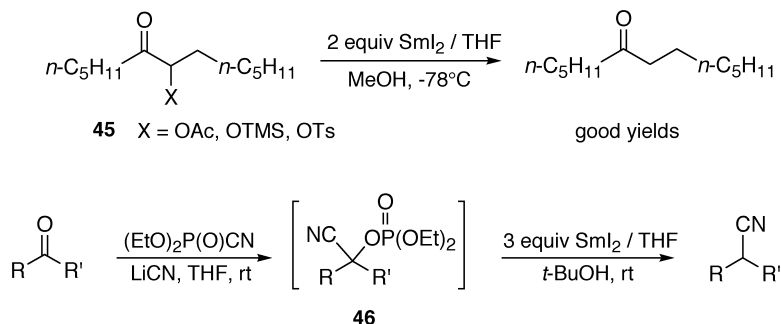
Scheme 54

been applied to conjugated enones or enals, giving β,γ-unsaturated nitriles without products from the migration of the double bond.

Aliphatic α-epoxy ketones were also successfully converted into the corresponding β-hydroxy ketones by SmI_2 in THF–methanol solution [133]. The protonation of the intermediate ketyls is the key step in the process. Radical •C(OH) generated vicinal to an epoxide induces α C–O bond cleavage with ring opening of the epoxide. The alkoxy radical is finally reduced to an alcoholate. Aliphatic α-epoxy ketones have also been treated with diiodosamarium in the presence or absence of methanol [134]. A large excess of methanol (or water) favored the formation of the β-hydroxy ketone, which is absent under aprotic conditions (in this case a small amount of α,β-diketone may be detected).

Deoxygenation reactions have been developed for the preparation of some deoxy sugars. A convenient procedure is to use SmI_2 in THF in the presence of anhydrous ethylene glycol as the proton source (Scheme 55).

Peracetylated aldonolactones gave mixtures of the unsaturated aldonolactone and the deoxy analog [135]. However, good control of the nature of the leaving group and the addition or non-addition of HMPA may fully control the selectivity of the reaction in the direction of the saturated or the unsaturated sugars [136]. Some examples are indicated in Scheme 55. A similar procedure has been used for the anomeric deoxygenation of peracetylated 2-ulosonic acids (as methyl esters) [137]. Deoxygenation in position α to a ketone has been successfully performed in the taxoid family [138].

Reduction of epoxy esters was not selective in the presence of methanol or ethanol but gave good yields of β-hydroxy esters by using *N,N*-dimethylethanolamine (DMEA) [40]. DMEA seems to play the role of a proton source and also acts as a chelator of samarium species, increasing the reduction power of SmI_2 and decreasing the Lewis acidity of Sm(III). See Scheme 56 for some examples.

R = H   (with HMPA):   72%
R = Ac (without HMPA): 94%

60%
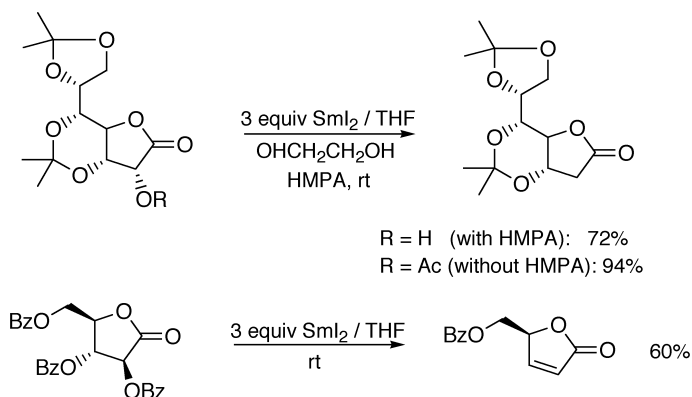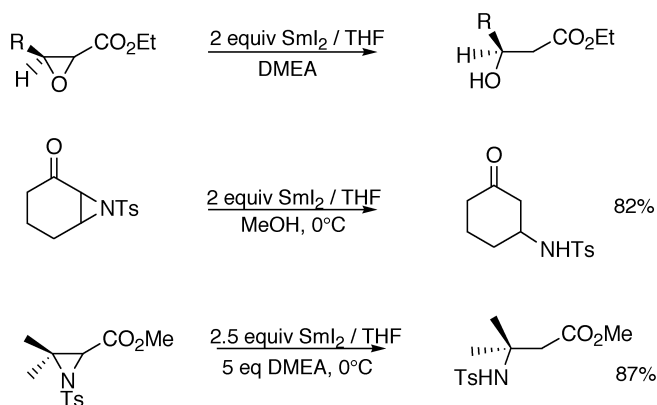
Scheme 55

Scheme 56

The reduction of 2,3-epoxycycloalkanone hydrazones by SmI_2 in THF in the presence of *t*-BuOH has been investigated by Kang et al. [139]. 2-Acylaziridines were converted into β-amino carboxyl compounds (Scheme 56) by a reaction very similar to the reduction of α,β-epoxy ketones [140]. The main problems were the unselective ring opening of the aziridine ring and the formation of over-reduced amino alcohols. These difficulties were overcome by using 2.5 equiv of SmI_2 in THF at 0 °C in the presence of a suitable proton source. In the case of 2-acylaziridines, methanol was preferred, while for aziridine-2-carboxylates and aziridine-2-carboxamides, DMEA was the best additive. The usefulness of DMEA may be related to several factors, as already pointed out by Inanaga et al. for the reduction of epoxy esters [40] (vide supra).

3.2.2.5
Conclusions

Protic additives other than water strongly modify the course of the reactions mediated by diiodosamarium. As discussed above, the additives protonate some anionic intermediates to new intermediates, driving the reaction in the desired direction. In some specific cases it may coordinate to samarium and modify the redox and Lewis acid properties of some of the samarium complexes. Chiral protic additives may also act as asymmetric protonating agents of prochiral intermediates. For example, Takeuchi et al. reduced benzil to the corresponding samarium enediolate and treated it with various chiral amino alcohols. The resulting benzoin could be obtained with ee's up to 91% by using quinidine as the proton source [141]. The catalytic use of a C_2-symmetric diol for asymmetric protonation of some samarium enolates was achieved in the presence of trityl alcohol (an achiral proton source for regeneration of the catalyst). In this way ee's up to 93% were observed [142]. Enantioselective protonation of samarium enolates

generated from 2-methoxy-2-substituted cyclohexanones by SmI_2 in the presence of some chelating chiral diols gave up to 94% ee of 2-substituted cyclohexanones [143,144]. The in situ asymmetric protonation of allenylsamariums obtained by reduction of propargylic esters has recently been described (see Sect. 3.3.6).

3.2.3
Acids

The combination of SmI_2 with a protic or aprotic acid ($POCl_3$, HCl, H_2SO_4 or H_3PO_4) has been investigated by Kamochi and Kudo for the reduction of aromatic acids and derivatives [145]. Excellent results were obtained by the addition of an amount of 85% H_3PO_4. Thus, at room temperature, acids or esters gave primary alcohols, while amides $ArCONH_2$ were transformed into aldehydes and aromatic nitriles into primary amines. All these reactions were performed in THF in a few minutes. In some cases there were some differences to the corresponding reduction in the presence of a base which was described in Sect. 3.1.4. A mechanism was proposed by the authors to explain the influence of acids, involving protonation of various intermediates.

Curran and Studer recently used 1 equiv of trifluoroacetic acid or BF_3–OEt_2 as a useful additive to promote the reductive coupling of aromatic dimethylacetals to 1,2-diaryl-1,2-dimethoxyethanes [112]. If the acids were replaced by water, a reductive demethoxylation occurred (see Sect. 3.2.1). The added acid may activate the acetal, giving formation of an oxocarbenium ion which is then reduced by SmI_2 to a radical which couples or is further reduced. It is interesting to note that a Lewis acid such as BF_3–OEt_2 is compatible with the use of SmI_2.

3.3
Metal Salts

3.3.1
Iron Salts

In 1980 we noticed that a samarium Barbier reaction between *n*-butyl iodide and 2-octanone which needed 8 h at 65 °C could be run in 3 h at room temperature in the presence of a catalytic amount (2 mol%) of ferric chloride [15]. This experiment was inspired by the known catalytic effect of the Fe^{3+} ion on the Ln^{2+}/Ln^{3+} conversion [146]. The beneficial influence of the Fe(III) derivative in reactions mediated by SmI_2 has been used by several authors in various processes. Thus, Molander et al. described a general procedure for five- and six-membered ring annulation starting from 2-(ω-iodoalkyl) cycloalkanones [147].

Diiodosamarium induced an intramolecular Barbier reaction, under mild conditions (room temperature), in the presence of a catalytic amount of iron tris(dibenzoylomethane [Fe(DBM)$_3$]. In this way many bicyclic tertiary alcohols were prepared. These conditions were also convenient for the cyclization
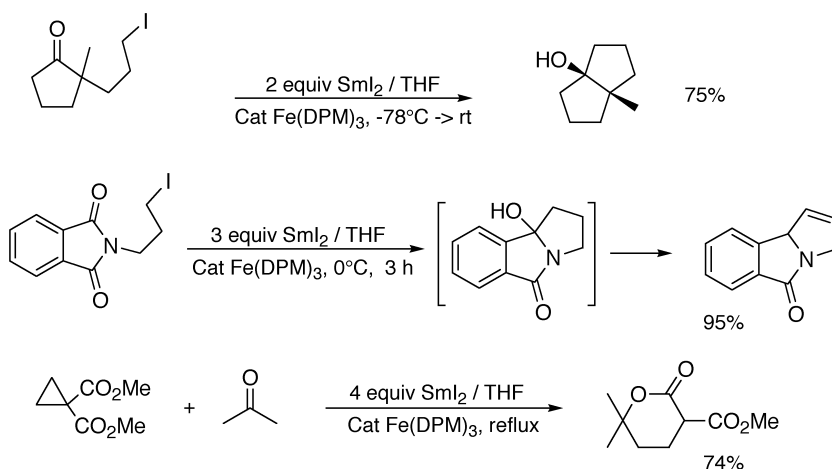
Scheme 57

of ω-iodoalkyl acyl derivatives (esters, lactones or amides) into ketones [148]. A comparison was made between addition of HMPA or of a catalytic amount of Fe(DBM)$_3$ or Fe(acac)$_3$. Both methods are often of the same efficiency. This type of reaction was named intramolecular nucleophilic acyl substitution of halo-substituted esters or lactones. One example is shown in Scheme 57. A similar cyclization involving *N*-iodoalkyl cyclic imides was later described by Ha et al. (see Scheme 57) [149] using SmI$_2$/*t*-BuOH. Iron(III) catalysis was also useful in the reductive cleavage of cyclopropanes activated by ester functions [150]. This cleavage may also be realized in the presence of an aliphatic ketone which traps the intermediate samarium homoenolate, one example is depicted in Scheme 57.

Iron(III) catalysis may be considered as a good alternative to HMPA activation in many reactions induced by SmI$_2$. Recently, we reinvestigated this area to discover whether other metal salts could be equivalent or superior. Diiodonickel was the result of this investigation (vide infra).

3.3.2
Nickel Salts

We screened the catalytic behavior of various transition-metal salts or complexes in the classical Barbier reaction between 2-octanone and 1-iodobutane in the presence of 2 equiv of SmI$_2$ in THF at room temperature [151]. Many metal halides significantly improved the yield (compared to the blank reaction): FeX$_3$ (X= Br, Cl, I), CuCl$_2$, CuI, NiX$_2$ (X=Br, I), AgX (X=Br, I), CoBr$_2$. Amongst them NiI$_2$ proved to be a superior catalyst allowing an almost quantitative reaction in less than 10 min. Surprisingly, acetylacetonates of Ni, Fe, Co and Cu are quite inefficient in this reaction.

Diiodonickel (1 mol%) accelerated significantly many of the reductions performed by SmI$_2$ in THF. For example, some epoxides were deoxygenated in good yields to the corresponding alkenes at room temperature in 20 min, 2-octanone gave the pinacol in 10 min (instead of 24 h without catalyst) at room temperature, and cyclohexane carbonyl chloride coupled quantitatively into 2-hydroxy-1,2-dicyclohexylethanone in 1 min (reaction performed in THP).

An unexpected feature of the SmI$_2$/NiI$_2$ system is the high reactivity of esters under intermolecular Barbier conditions. As for Grignard reagents, the reaction gives tertiary alcohols; one example is mentioned in Scheme 58. The coupling between a ketone and a conjugated ester, which is promoted by HMPA [38], may be easily obtained by NiI$_2$ catalysis (Scheme 58). Nucleophilic acylation of esters by acid chlorides has been realized by the Barbier procedure (Scheme 58) [152]. The reaction intermediate **A** can be either hydrolyzed into mixed α-ketols or quenched by other electrophiles (aldehydes or anhydrides). Recently, NiI$_2$ catalysis has been successfully applied to the cyclization of iodoalkyl α,β-unsaturated esters or amides (for one example, see Scheme 58); iron(III) catalysts were equally efficient [153]. NiI$_2$ has also been used to selectively activate 1-iodo-3-chloropropane for the Barbier condensation on various keto esters, the reaction occurring on the carbon bearing the iodine [154].

Scheme 58

3.3.3
Cobalt Salts

In 1991, Inanaga et al. described the reduction at room temperature of some disubstituted alkynes by the combination SmI_2/proton source in the presence of some transition-metal catalysts (3% equiv) in THF [155]. By a good choice of catalyst ($CoCl_2$, 4 PPh_3) and proton source (MeOH, i-PrOH or AcOH) it was possible to orientate the reaction towards the exclusive formation of the Z-alkene. When the same reaction was performed in the presence of HMPA then the E-alkene was produced. Iron(III) and Ni(II) catalysts were found to be less efficient. It was assumed that the reactive species were the corresponding transition-metal hydrides obtained by reduction of the initial complexes.

3.3.4
Copper Salts

When copper salts were added to organosamarium species produced in situ from an organic halide and SmI_2, a transmetallation process gave organocoppers able to react in catalyzed conjugate additions [156,157].

The cross-coupling of alkylsamarium reagents with alkyl halides may be catalyzed by copper salts such as CuX (X=Br, Cl or I) or Li_2CuCl_4 [158]. The most effective catalyst for the desired cross-coupling was CuBr or Li_2CuCl_4. The reaction was performed at room temperature in THF with 8 equiv of HMPA. Some examples are listed in Scheme 59. In order to optimize cross-coupling products R^1–R^2, the reaction was performed in two steps, with initial formation of the organosamarium from R^1X and then addition of the catalyst and of R^2X.

3.3.5
Chromium Salts

Alkylation of ketones by gem-dibromoalkanes in the presence of a stoichiometric amount of SmI_2/Sm (1:1) and a catalytic amount of $CrCl_3$ (10% equiv) was studied by Utimoto et al. [159]. It gave in moderate yields (40–70%) various

Ph—C≡C−n-Bu $\xrightarrow{\substack{\text{2.5 equiv } SmI_2 \text{ / THF} \\ \text{MeOH, rt} \\ \text{3\% equiv } CuCl_2 \cdot 4 PPh_3}}$ H H / Ph n-Bu   97% $Z / E > 99 : 1$

n-C_7H_{15}Br $\xrightarrow{\substack{\text{2.5 equiv } SmI_2 \text{ / THF} \\ \text{8.3 equiv HMPA, 15 min, rt}}}$ $\xrightarrow{\substack{\text{2\% equiv CuBr} \\ \text{5 min, rt}}}$ n-C_6H_{13}I $\xrightarrow{\substack{\\ \text{15 min, rt}}}$ R^1— R^2 87% $R^1 = n$-C_7H_{15} $R_2 = n$-C_6H_{13}
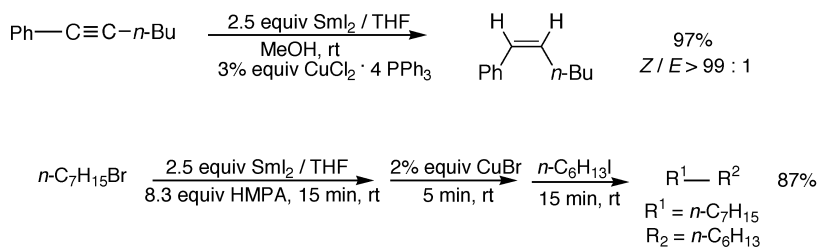
Scheme 59

alkenes as *E/Z* mixtures. The reaction presumably involves a *gem*-dimetallic reagent [C(SmX$_2$)$_2$ or C(SmX$_2$)(CrX$_2$)]. The reaction can be applied to easily enolizable ketones such as β-tetralone.

3.3.6
Palladium Complexes

In 1986 Inanaga et al. found that allylic or propargylic acetates could be reduced in THF by diiodosamarium in the presence of a catalytic amount of a Pd(0) complex and 1 equiv of 2-propanol [160,161]. Some examples are indicated in Scheme 60. The mechanism of the reaction likely involves π-allyl (or σ-allenyl) palladium intermediates which are reduced first to radicals and then to carbanions (see Scheme 60). A final protonation by the alcohol generates the products.
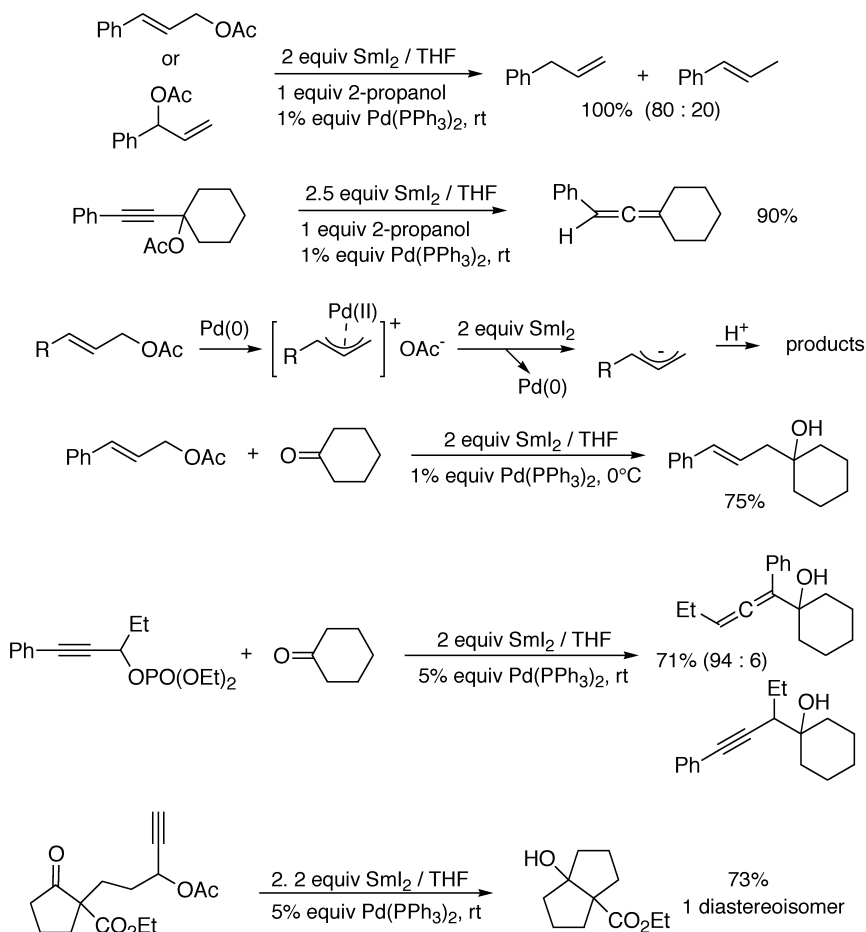
Scheme 60

Some limitations to this reaction have been noticed [162]. The reductive coupling of allylic acetates with carbonyl compounds (which act as electrophiles in replacement of a proton donor) provided homoallylic alcohols [163]. Similarly, coupling of propargylic esters to carbonyl compounds gave allenyl alcohols or acetylenic alcohols according to the structure of the reactants [164,165]. Some examples can be found in Scheme 60. The intramolecular coupling reaction using ω-keto-alkynyl esters allowed the synthesis of five- or six-membered ring systems [166]. A highly regio- and stereoselective synthesis of allylsilanes was achieved by reductive silylation of allylic phosphates with a SmI$_2$/HMPA/Pd(0) system and TMSCl [167].

A regiodivergent reduction of allylic esters with SmI$_2$ in the presence or absence of a Pd(0) catalyst gave either α- or γ-protonated products by tuning the proton source (alcohols, H$_2$O) and the ester functionality (Scheme 61) [168].

A changeover of regioselectivity was observed by Mikami et al. in the reduction of secondary propargylic phosphates by the SmI$_2$/Pd(0)/proton source system [169]. *tert*-Butanol and dimethyl (*R,R*)-tartrate gave allene and acetylene, respectively (Scheme 61). This process was modified in an asymmetric synthesis of chiral allenes [170].

2,3-Naphthoquinodimethanes were easily generated from *ortho*-bis(α-acetoxypropargyl) benzene derivatives by the SmI$_2$/Pd(0)/proton donor system [171]. The reduction occurs by a 6π-electron cyclization of an *O*-diallenylbenzene intermediate.

3.3.7
Lithium Salts

The Barbier reaction discussed in Sect. 3.3.2 was not accelerated by addition of LiCl. In the literature there are only a few examples where lithium salts are ben-
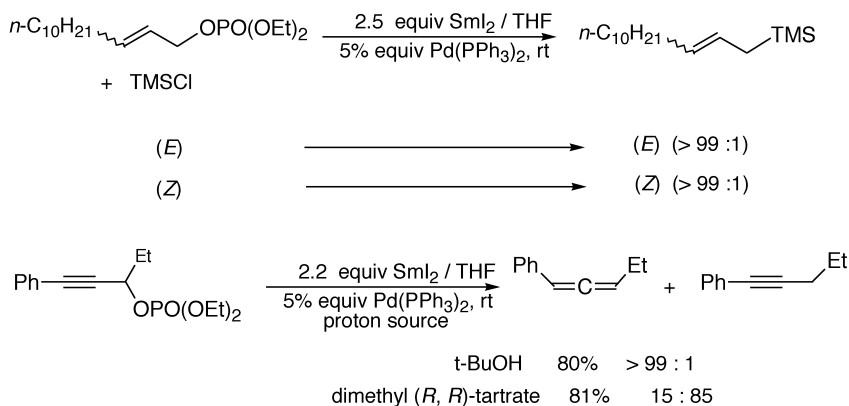
Scheme 61
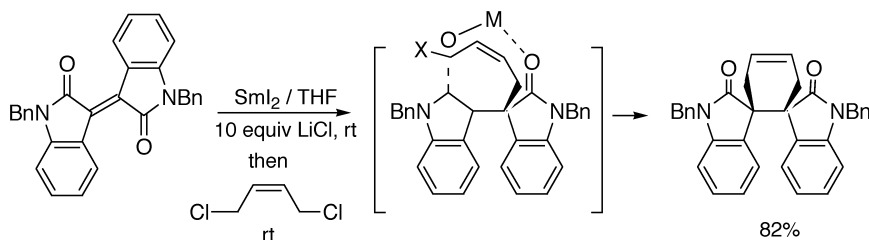
Scheme 62

eficial for reactions mediated by SmI_2. However, it is worth mentioning that a reductive dialkylation of isoindigo by *cis*-1,4-dichloro-2-butene only works in the presence of an excess of LiCl (KCl is inefficient) as indicated in Scheme 62 [172]. The mechanism was not elucidated; a chelate may be involved.

Recently, Flowers et al. initiated a study on the influence of additives on the reactivity of SmI_2, in parallel with electrochemical investigations (see Sect. 3.1.1). These authors found that the oxidation potentials of SmI_2 in THF containing 12 or more equivalents of LiBr or LiCl were, respectively, –1.98 and –2.11 V (instead of –1.33 V). They established that the corresponding molecular species were not $SmBr_2$ and $SmCl_2$. These new reagents are highly reactive and facilitate the pinacol coupling of cyclohexanone at room temperature in a few minutes at room temperature [173].

4
Conclusions

In this chapter we have tried to present the main changes which occur for reactions mediated by diiodosamarium when THF is replaced by other solvents or when some additives are introduced into the THF solution. Many useful organic transformations have been achieved by this approach but, due to lack of space, this area has not been covered extensively. However, we hope to have demonstrated that introduction into THF of various additives in stoichiometric or catalytic amounts or replacement of THF by another solvent may drastically modify the behavior of SmI_2. The most promising approach involves the use of molecular catalysts since one may expect a wide range of chemo- or stereoselectivities by suitable changes in the structure of the catalysts.

5
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Chiral Heterobimetallic Lanthanoid Complexes: Highly Efficient Multifunctional Catalysts for the Asymmetric Formation of C-C, C-O, and C-P Bonds

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The use of alkali metal-containing, heterobimetallic lanthanoid complexes as catalysts in asymmetric synthesis is reviewed. This new and innovative type of chiral catalyst, which was recently developed by Shibasaki et al., contains a Lewis acid as well as a Brønsted base moiety, thereupon showing a similar mechanistic effect as observed in enzyme chemistry. The heterobimetallic complexes have been successfully applied as highly stereoinducing catalysts in many different types of asymmetric reactions, including the stereoselective formation of C-C, C-O, and C-P bonds.

Keywords: Heterobimetallic catalysts, Lanthanoid complexes, Asymmetric synthesis, Homogenous catalysis

Abbreviations

Ln   lanthanoid metal ion (III)
M   alkali metal ion
L   lithium
S   sodium
P   potassium
B   1,1'-binaphthol (BINOL)
LnMB   lanthanoid-alkali metal-binaphthoxide complex of type LnM_3tris(binaphthoxide)
LLB   lanthanum-lithium-binaphthoxide complex $LaLi_3$tris(binaphthoxide)

1
Introduction

One of the most fascinating aspects in the history of asymmetric catalysis with its countless successful applications in the stereoselective synthesis of a broad variety of functional groups is the structural variety of the complexes which are able to be used as catalysts [1, 2]. Many catalysts have been developed based on different ideas and concepts of mechanistic effect. However, in spite of the abundance of such catalysts which have been successfully applied in asymmetric catalysis, not a handful of them possess multifunctional abilities catalyzing different type of enantioselective reactions. The development of such a type of chiral catalyst, the catalytic effect of which is not limited to one reaction but to different types of asymmetric synthetic organic transformations, remained an attractive challenge for a long time.

In the following, such a desired new and innovative multifunctional catalytic system is reviewed: The chiral heterobimetallic lanthanoid complexes, developed by Shibasaki et al., have recently been shown to catalyze a broad spectra of organic reactions including many "classical" carbon-carbon bond formations

like the nitroaldol reaction, Michael addition, aldol reaction and so on, but also an oxidation reaction as well as the asymmetric formation of carbon-phosphorus bonds with excellent stereoselectivity in all cases (Fig. 1) [3–5]. This new concept for catalytic asymmetric reactions, based on the idea of using chiral heterobimetallic lanthanoid complexes which function as both Brønsted base and Lewis acid, just like an enzyme, makes possible a variety of efficient catalytic asymmetric reactions.

2
Structural Requirements for an Efficient Bimetallic Catalyst: What does the Catalysts Look Like?

For a better understanding of many successful applications of the rare earth-alkali metal containing LnM_3tris(binaphthoxide) complexes (LnMB, Ln=rare earth, M=alkali metal) to catalytic asymmetric synthesis, intense investigations also focused on the determination of the structure. It has been shown that these complexes, which can be readily prepared from the corresponding rare earth trichlorides and/or rare earth isopropoxides [5], possess a structure as presented in Fig. 2. This structure was supported by various NMR spectroscopic, MS spectrometric, X-ray crystallographic and other analytic investigations of a variety of LnMB complexes.

Beginning with LDI-TOF mass spectral analysis, these investigations revealed that the structure was in fact a heterobimetallic complex consisting of one lanthanum, three lithium and three BINOL moieties [6]. Although LDI-TOF mass
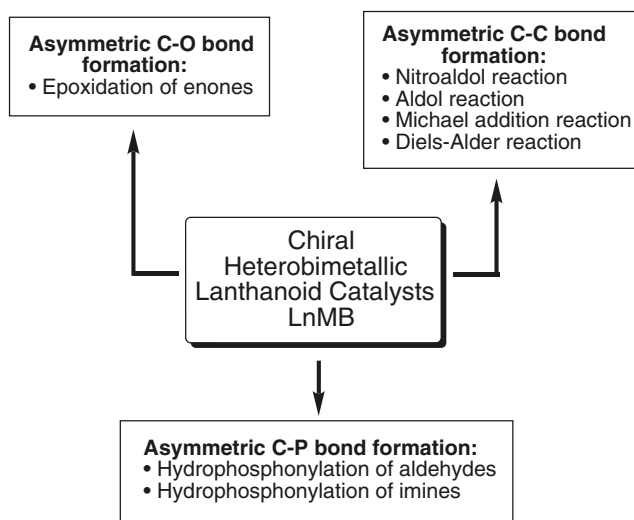
Figure 1. Applications of heterobimetallic lanthanoid complexes in asymetric catalysis
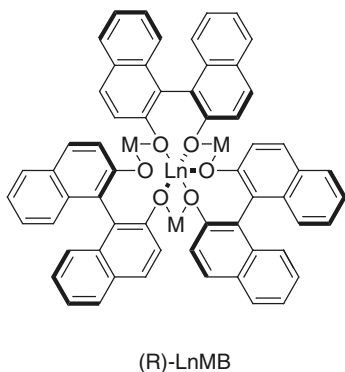
(R)-LnMB

Figure 2. The structure of (R)-LnMB. (M=alkali metal, Ln=lanthanoid metal)

spectrometry has a mass accuracy of about ±0.1%, the proposed structural framework was strongly supported by the similarity of the mass spectra of various other rare earth complexes, since rare earth elements have their own atomic weights and isotope abundance distributions. Successful attempts have also been made to obtain X-ray grade crystals of rare earth complexes of type LnLB and LnSB [6–8]. Several rare earth-sodium-BINOL complexes (LnSB, S=sodium) could be crystallized from THF starting from rare earth trichlorides including LaCl$_3$, disodium (R)-binaphthoxide, NaOtBu, and H$_2$O. The elemental analyses suggested a stoichiometry of LnNa$_3$tris(binaphthoxide)-6THF-2H$_2$O, which was confirmed by X-ray crystallographic analyses of La, Pr, Nd, and Eu complexes as being correct. The X-ray crystallographic analyses showed that these crystals had almost the same structure (Fig. 2), with the differences being in the distance of the atoms around the center from the central rare earth metal [6, 7]. Each rare earth (S)-BINOL complex has a chiral center at the rare earth metal so that the (S)-BINOL complex can exist as a diastereomer. Nevertheless, it is interesting to note that La, Pr, Nd, and Eu complexes starting from (S)-BINOL exist only in the Λ-configuration, perhaps due to the greater thermodynamic stability of this configuration compared to the Δ-form.

All the above-mentioned LnSB crystals showed similar mass patterns compared to those of Ln-Li-BINOL complexes, though they contained sodium instead of lithium. The oligomeric structure of the catalysts in the reaction mixture was supported by a slightly positive asymmetric amplification in the asymmetric nitroaldol reaction [9]. In addition, quite recently Shibasaki et al. reported the first X-ray crystallographic structure of a lithium-containing heterobimetallic catalyst of type LnLB, namely the SmLi$_3$tris(binaphthoxide) complex SmLB [8].

Concerning the heterobimetallic potassium lanthanoid catalysts (R)-LnPB, a very recent NMR spectroscopic as well as FAB and ESI mass spectrometric study of isolated (R)-YbPB complexes provided a clear insight into the assembly of this heterobimetallic complex in solution. At first, the assumption that the proposed

structure of *(R)*-YbPB (according to Fig. 2) corresponds with those of isolated crystals *(R)*-YbPB was confirmed [10]. Moreover, the application of these isolated crystals *(R)*-YbPB in an asymmetric hydrophosphonylation reaction (see also Sect. 5.2.2.) gave (nearly) the same good result as the corresponding catalyst solution, indicating that the determined structure of the crystals corresponds with the actual catalytically active species. Such a knowledge of the composition of the heterobimetallic catalysts, namely the potassium derivative *(R)*-YbPB, in solution represents one of the rare cases in catalytic asymmetric synthesis in which the "real catalytically active species" could be isolated, applied, and analyzed by NMR spectroscopical and mass spectrometrical methods.

In summary, it is noteworthy that all of these heterobimetallic asymmetric complexes of type LnMB are stable in organic solvents such as THF, CH_2Cl_2 and toluene which contain small amounts of water, and also are insensitive to oxygen. Using a catalytic amount of LnMB complexes various kinds of asymmetric C-C bond formation reactions, an asymmetric epoxidation, and asymmetric hydrophosphonylations of either imines or aldehydes (catalyzed by LnPB, P=potassium) proceed efficiently to give the corresponding desired products in high stereoselectivity. In detail, these asymmetric reactions will be discussed in the following sections.

3
Asymmetric Catalytic C-C Bond Formation Using Heterobimetallic Lanthanoid Complexes

3.1
Nitroaldol Reaction

3.1.1
Development of an Efficient Catalysis in Model Reactions

In 1992, Shibasaki et al. reported for the time an application of chiral heterobimetallic lanthanoid complexes (LnLB) as chiral catalysts in asymmetric catalysis, namely the catalytic asymmetric nitroaldol reaction (Henry reaction), which is one of the most classical C-C bond forming processes [11]. Additionally, this work represents the first enantioselective synthesis of β-nitroalcohol compounds by the way of enantioselective addition of nitroalkanes to aldehydes in the presence of a chiral catalyst. The chiral BINOL based catalyst was prepared starting from anhydrous $LaCl_3$ and an equimolar amount of the dialkali metal salt of BINOL in the presence of a small amount of water [9].

Starting from prochiral aldehydes **1–3**, the desired products b were obtained in good chemical yields and with enantioselectivities up to 90% ee (Scheme 1) [11]. The amount of the catalyst is not shown in Scheme 1 due to the unknown structure of the catalyst (at this time).

Investigations concerning the influence of the rare earth metal component showed pronounced differences both in the reactivity and in the enantioselec-

RCHO   +   CH₃NO₂ $\xrightarrow[\text{THF, -42 °C, 18 h}]{\text{La-Li-(S)-BINOL complex}}$ R–CH(OH)–CH₂NO₂

(10 equiv)

1: R = PhCH₂CH₂   **4**: 79% (73% ee), R = PhCH₂CH₂
2: R = iPr   **5**: 80% (85% ee), R = iPr
3: R = cyclohexyl   **6**: 91% (90% ee), R = cyclohexyl
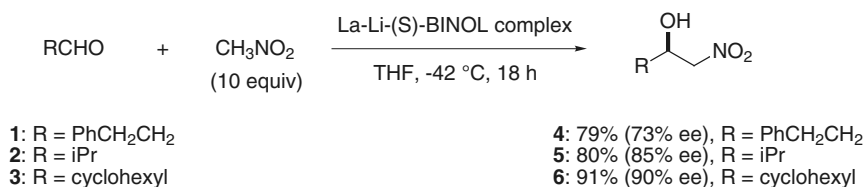
Scheme 1. The first catalytic asymmetric nitroaldol reaction catalyzed by chiral lanthanoid complexes.
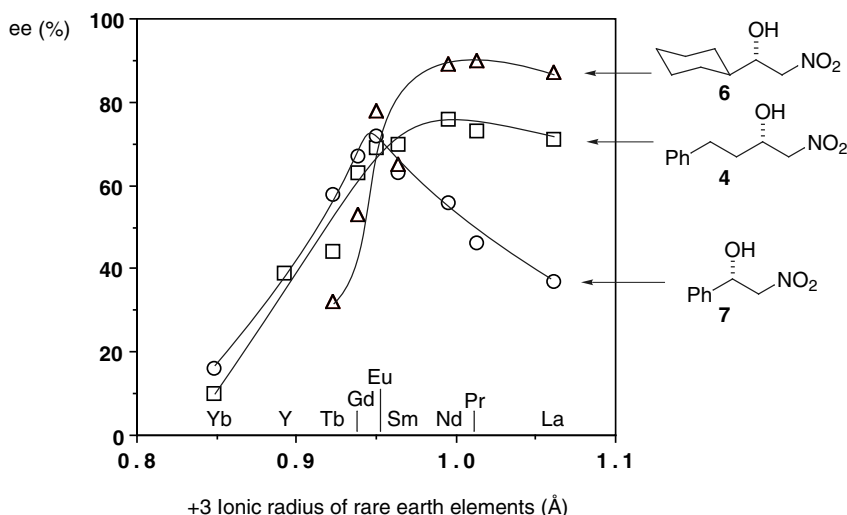
Figure 3. Effects of the ionic radii of rare earth elements on the enantioselectivity.

tivity among the various rare earth metals used [12]. When benzaldehyde and nitromethane were used as starting materials, the corresponding Eu complex gave **7** in 72% ee (91%) in contrast to 37% ee (81%) in the case of the La complex (–40 °C, 40 h). The unique relationship between the ionic radii of rare earth metals and the enantioselectivities of several nitroaldols **4, 6, 7** are depicted in Fig. 3.

Consequently, small changes in the structure of the catalyst (ca. 0.1 Å in ionic radius of the rare earth cation) cause drastic changes in the optical purity of the produced nitroaldols. Although in general nitroaldol reactions are regarded as equilibrium processes, no detectable retro-nitroaldol reaction was observed in the Ln-BINOL complex catalyzed asymmetric nitroaldol reactions.

The proposed mechanism for the asymmetric nitroaldol reaction catalyzed by heterobimetallic lanthanoid complexes is shown in Scheme 2 [5]. In the initial step, the nitroalkane component is deprotonated and the resulting lithium nitronate coordinates to the lanthanoid complex under formation of the inter-
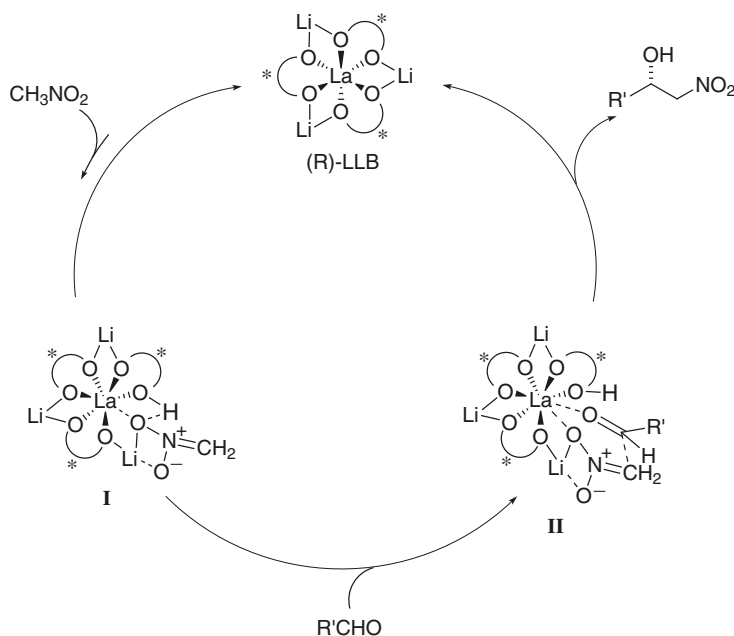
Scheme 2. A possible mechanism for catalytic asymmetric nitroaldol reactions with nitromethane.

mediate I. [13] Subsequent addition of the aldehyde by coordination of the C=O double bond to the lanthanoid (III) center ion leads to intermediate II, in which the carbonyl function should be attacked by the nitronate via a six-membered transition state (in an asymmetric environment). A proton exchange reaction step will then generate the desired optically active nitroalkanol adduct with regeneration of the "free" rare earth complex LnLB.

In addition to the early results of the general and effective catalytic asymmetric nitroaldol reaction (Scheme 1), which proceeds efficiently in the presence of 3.3 mol% of LLB, the knowledge of the structure of the LnLB complexes (see Sect. 2) led to an extension of this catalytic method to a wide range of further applications which are described below.

The structural modification of the BINOL ligand system also plays an important role concerning stereoselection in the asymmetric Henry reaction. Improved enantioselectivites were obtained using a number of *(R)*-BINOL derivatives in which the 6,6'-positions were substituted [14]. Their utility as asymmetric catalysts was assessed with enantioselectivities up to 88% ee accompanied by chemical yields up to 85% in the nitroaldol reaction of nitromethane with hydrocinnamaldehyde **1**. Whereas the substitution at the 6,6'-position of BINOL proved to be effective in obtaining superior asymmetric catalysts, the use of complexes derived from 3,3'-disubstituted BINOL derivatives [15, 16] gave racemic **4** and BIPOL derived catalyst [17] gave **4** in only 39% ee.

Recently, Okamoto et al. showed that the reactivity and selectivity also depends on the alkali metal component in the heterobimetallic catalysts [18]. Using the bulkier 2-nitropropane as starting material in a model reaction with benzaldehyde, almost no reaction occurred at –30 ˚C in the presence of the lithium containing catalyst LLB, whereas higher temperatures as well as the use of HMPA as a co-solvent only led to racemic product. However, in the presence of the corresponding potassium-containing catalyst LPB the desired reaction proceeded with 46% ee. In contrast, the use of LLB was connected with superior enanioselectivity and chemical yield (compared to LPB) when replacing 2-nitropropane by the less bulkier nitromethane (LLB: 91% yield; 48% ee; LPB: 71% yield; 6% ee) [18].

3.1.2
Enantioselective Catalytic Nitroaldol Reaction: Adducts with One Stereogenic Center

A first example of an efficient application of the LnLB catalyzed nitroaldol reaction as key step in a multi-step syntheses was presented by Shibasaki et al. in the asymmetric approach to three kinds of optically active β-blockers **10, 13**, and **16** (Scheme 3) [12, 19–21].

Using **14** and 10 mol equiv of nitromethane at –50 ˚C in the presence of 3.3 mol% of *(R)*-LLB catalyst, a 76% yield of nitroaldol **15** in 92% ee was obtained. Reductive alkylation of the nitroaldol **15** to **16** was accomplished by a PtO$_2$ catalyzed hydrogenation. Thus, *(S)*-(–)-pindolol **16** was synthesized in only four steps from 4-hydroxyindole [20]. Interestingly, the nitroaldols **9, 12**, and **15** were found to have *(S)*-configuration when *(R)*-LLB was used. The nitronates thus appear to react preferentially with the Si face of the aldehydes, in the oppo-
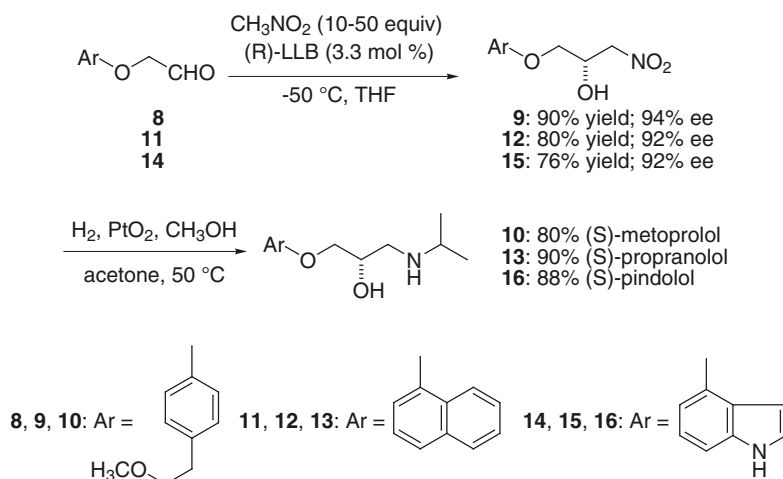
Scheme 3. Catalytic asymmetric synthesis of β-blockers using *(R)*-LLB as a catalyst.

site sense to the enantiofacial selectivity which might have been expected on the basis of the previous results (cf. Scheme 1). These results suggested that the presence of an oxygen atom at the β-position had a pronounced influence on the enantiofacial selectivity.

The LLB type catalysts were also successfully applied in the asymmetric nitroaldol reaction of quite unreactive α,α-difluoro aldehydes. However, catalytic asymmetric nitroaldol reaction of a broad variety of α,α-difluoro aldehydes proceeded satisfactorily when using the heterobimetallic asymmetric catalysts with modified, 6,6'-disubstituted BINOL ligands [22]. The best results were obtained with the samarium (III) complex (5 mol%) generated from 6,6'-bis{(triethylsilyl)ethynyl}BINOL with enantioselectivities up to 95% ee. The *(S)*-configuration of one representative nitroaldol adduct showed that the nitronate reacted preferentially on the Si face of aldehyde in the presence of *(R)*-LLB (20 mol%; 74% yield; 55% ee). It is noteworthy that the enantiotopic face selection for α,α-difluoro aldehydes is reverse to that for nonfluorinated aldehydes. The stereoselectivity for α,α -difluoro aldehydes is identical with that of β-oxa-aldehydes, suggesting that the fluorine atoms at the α-position have a great influence on enantioface selection.

3.1.3
Diastereoselective Catalytic Nitroaldol Reaction Starting from Chiral Aldehydes

The diastereoselective catalytic nitroaldol reaction has been investigated starting from optically active α-amino aldehyde, e.g. **17**. The adducts of type **18** are attractive intermediates for the synthesis of unnatural erythro-amino-2-hydroxy acids, which are important components of several biologically active compounds. For example, the promising HIV-protease inhibitor KNI-272 [23, 24] contains *(2S,3S)*-3-amino-2-hydroxy-4-phenylbutanoic acid (erythro-AHPA, **19**) as a subunit. A conventional diastereoselective synthesis in the presence of achiral bases led to limited internal induction with *erythro/threo* ratios of **18** in the range between 62:38 and 74:26. The use of the achiral complex La(O^{i}Pr)$_3$ gave the product **18** in an 89:11 *erythro/threo* ratio [25]. However, this limitation of diastereoselection has been overcome using catalytic amounts of lithium-containing heterobimetallic complexes LnLB (Scheme 4).

In the presence of *(R)*-LLB (3.3 mol%), the treatment of *N*-phthaloyl-L-phenylalanal **17** with nitromethane at –40 ˚C gave practically a single stereoisomer of *(2R,3S)*-2-hydroxy-4-phenyl-3-phthaloylamino-1-nitrobutane **18** in 92% yield (>99:1 *erythro*-selectivity) [25]. Interestingly, reaction of the *(S)*-aldehyde **17** with nitromethane, using the *(S)*-LLB complex as a catalyst, led to a reduced diastereo- and enantioselectivity (96% yield; *erythro/threo* 74:26; 90% ee(*erythro*)). The conversion of the nitroaldol adduct **18** into **19** was achieved in one pot (80% yield).

A further example of a diastereoselective nitroaldol reaction using heterobimetallic lanthanoid complexes as catalysts was recently reported by Okamoto et al. [18] in connection with a novel approach to 1α,24*(R)*-dihydroxyvitamin D$_3$
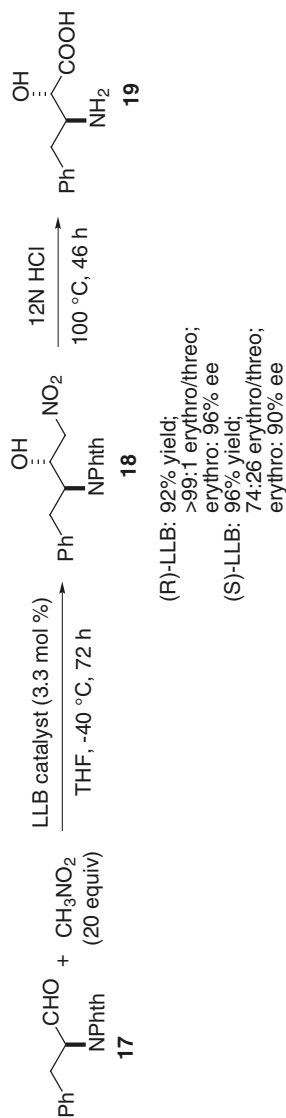
Scheme 4. Diastereoselective nitroaldol reaction as key step in the synthesis of *erythro*-AHPA **19**.
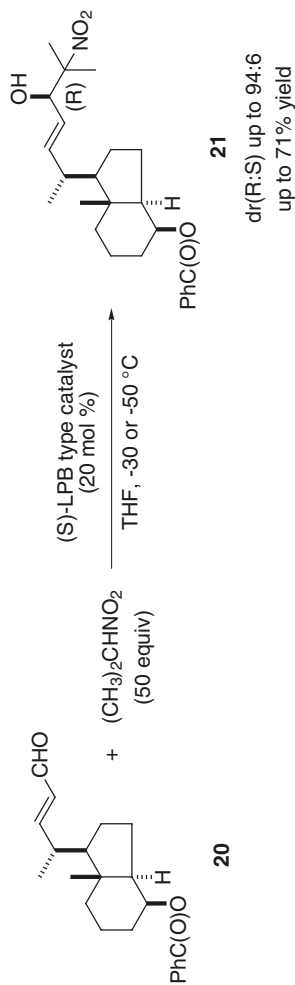
Scheme 5. Catalytic diastereoselective nitroaldol reaction promoted by the LPB type catalyst.

[26], which is an active analogue of vitamin D_3 and induces keratinocyte differentiation [27, 28]. Herein, several rare earth metal complexes were used to catalyze the nitroaldol reaction of the CD-ring 24-aldehyde precursor **20** with 2-nitropropane (Scheme 5). In accordance with the results of the corresponding model reaction with benzaldehyde when using 2-nitropropane as starting material (see Sect. 3.1.1.), the best results were achieved in the presence of the potassium containing lanthanoid complex of type LPB with *(S)*-6,6'-{(triethylsilyl)ethynyl}BINOL as ligand. The desired nitroaldol adduct **21** was formed in yields up to 71% and with diastereomeric ratios dr up to 94:6 (Scheme 5). It is noteworthy, that a conjugate double bond in the aldehyde component was needed for good asymmetric induction.

3.1.4
Diastereoselective and Enantioselective Nitroaldol Reaction

LnLB type catalysts are also able to promote diastereoselective and enantioselective nitroaldol reactions starting from prochiral materials. In preliminary work, LLB gave unsatisfactory results in terms of both diastereoselectivity (*syn/anti* ratio 63 : 37 to 77 : 23) and enantioselectivity (<78% ee) [19]. However, an effective asymmetric induction was obtained in the presence of LL(B-a) type catalysts containing 6,6'-substituted BINOL (Scheme 6; for the structure of B-a, see Scheme 7).

The application of the catalysts of type LL(B-a) (3.3 mol%) to diastereoselective nitroaldol reactions led to high *syn*-selectivity and enantioselectivity [29]. In all cases, much higher *syn*-selectivity (*syn/anti* ratio up to 94:6) and enanti-

RCHO + R'CH$_2$NO$_2$

catalyst (3.3 mol %)
THF, –40 °C

1 R = PhCH$_2$CH$_2$
22: R = CH$_3$(CH$_2$)$_4$

23: R' = Et
24: R' = CH$_2$OH

25(syn), **26** (anti): R = PhCH$_2$CH$_2$, R' = Et
27(syn), **28** (anti): R = PhCH$_2$CH$_2$, R' = CH$_2$OH
29(syn), **30** (anti): R = CH$_3$(CH$_2$)$_4$, R' = CH$_2$OH
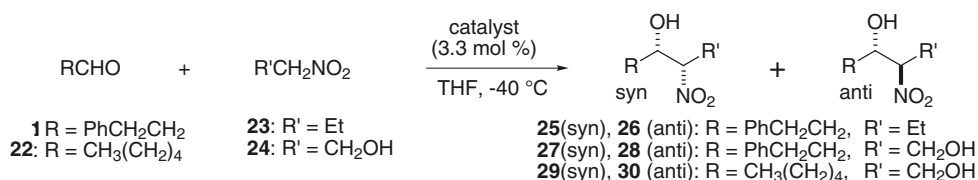
Reagent	Catalyst	Time [h]	Product	Yield [%]	*syn/anti*	ee (*syn*) [%]
1 + 23	LLB	138	**25 + 26**	89	85 : 15	87
1 + 23	LL(B-a)	138	**25 + 26**	85	93 : 7	95
1 + 24	LLB	111	**27 + 28**	62	84 : 16	66
1 + 24	LL(B-a)	111	**27 + 28**	97	92 : 8	97
22 + 24	LLB	93	**29 + 30**	79	87 : 13	78
22 + 24	LL(B-a)	93	**29 + 30**	96	92 : 8	95

Scheme 6. Diastereoselective and enantioselective nitroaldol reaction.
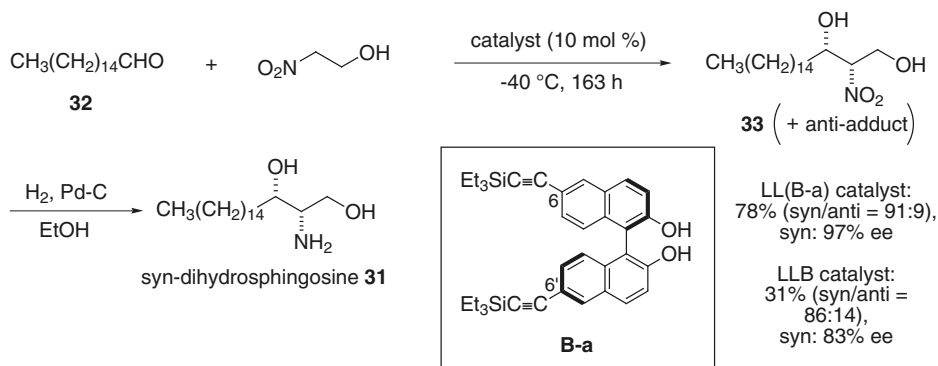
Scheme 7. Catalytic asymmetric synthesis of *syn*-dihydrosphingosine.

oselectivity (up to 97% ee) was obtained using the catalysts with 6,6'-substituted BINOL instead of LLB (for comparison representative results are given in Scheme 6). The optical purities of the minor anti-adducts **26**, **28**, and **30** were lower than those of the *syn*-adducts **25**, **27**, and **29**, indicating that the former were not generated by epimerization of the nitro group. In fact, treatment of the *syn*-adducts with catalysts such as LLB and its derivatives resulted in near-quantitative recovery of the starting materials with unchanged optical purities.

The *syn*-selective asymmetric nitroaldol reaction was successfully applied to the catalytic asymmetric synthesis of *threo*-dihydrosphingosine **31**, which elicits a variety of cellular responses by inhibiting protein kinase C (Scheme 7) [30]. Nitroaldol reaction of hexadecanal **32** with 3 equiv of nitroethanol catalyzed by LL(B-a) gave the corresponding nitroaldol adduct **33** in high syn-selectivity (91:9) and 78% yield, with the *syn*-adduct **33** being obtained with up to 97% ee [29]. In this case, under similar conditions the LLB-catalyzed reaction proceeded only slowly to give an 86:14 ratio of the syn and *anti*-adducts in 31% yield (with lower optical purity: 83% ee). The hydrogenation of **33** in the presence of 10% Pd on charcoal afforded *threo*-dihydrosphingosine **31** in 71% yield.

3.1.5
Tandem Inter-Intramolecular Catalytic Asymmetric Nitroaldol Reaction

The asymmetric catalytic nitroaldol reaction was furthermore successfully extended to the field of asymmetric tandem reactions [31]. Tandem reactions are especially useful to construct compounds with several chiral centers in a one-pot synthesis starting from simple achiral components in the presence of a chiral catalyst. The first tandem inter-intramolecular catalytic asymmetric nitroaldol reaction has been realized in the reaction of the cyclopentanedione derivative **34** with nitromethane using a catalytic amount of LnLB according to Scheme 8 [31].
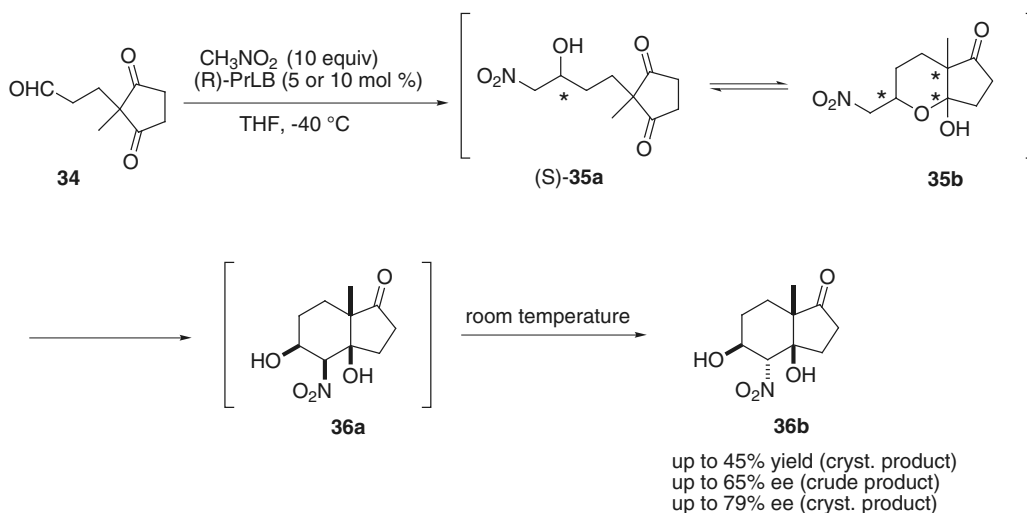
Scheme 8. Tandem inter-intramolecular catalytic asymmetric nitroaldol reaction.

In addition to temperature effects, the optical purity of the product **36b** strongly depends on the lanthanoid center ion. In the presence of *(R)*-PrLB complex (5 mol%) as the most efficient catalyst, the hexahydro-1-indanone derivative **36b** was formed with enantioselectivities up to 65% ee (for comparison: LLB (10 mol%; –20 °C): 39% ee; YbLB (10 mol%; –20 °C): 7% ee) [31]. After crystallization, **36b** was isolated with up to 79% ee and 41% yield.

3.1.6
Recent Improvements (Second Generation of LnLB Catalyst) and Summary

The catalytic asymmetric nitroaldol reactions promoted by LLB or its derivatives require at least 3.3 mol% of asymmetric catalysts for efficient conversion. However, even in the case of 3.3 mol% of catalyst, reactions are rather slow. Attempts were made to reduce the required catalytic amount and accelerate the reactions, which led to a second-generation heterobimetallic lanthanoid catalyst (LLB-II), prepared from LLB, 1 mol equiv of H_2O, and 0.9 mol equiv of butyllithium. The use of only 1 mol% of LLB-II efficiently promoted catalytic asymmetric nitroaldol reactions and additionally LLB-II (3.3 mol%) accelerated these reactions [32]. A comparison of the efficiency of LLB (or LL(B-a)) and the second-generation catalysts LLB-II (or LL(B-a)-II) is given in Scheme 9. The structure of LLB-II has not yet been unequivocally determined. However, it appears that it is a complex of LLB and LiOH.

Using a second-generation LnLB catalyst consisting of 6,6'-bis{(trimethylsilyl)ethynyl}BINOL and Sm, an efficient catalytic asymmetric synthesis of arb-

Scheme 9. Comparison of the catalytic activity of LLB and second-generation LLB (LLB-II) or LL(B-a) and LL (B-a)-II. [LLB-II: LLB + H$_2$O (1 mol equiv) + BuLi (0.9 mol equiv.); LL(B-a)-II: LL(B-a) + H$_2$O (1 mol equiv) + BuLi (0.9 mol equiv)]; For the structure of the BINOL derivative ligand B-a, see Scheme 7
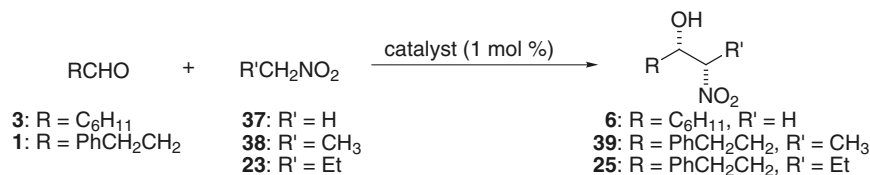
Reagent	Catalyst	Time [h]	Temp. [°C]	Product	Yield [%]	syn/anti	ee (syn) [%]
3 + 37	LLB	24	–50	6	5.6	–	88
3 + 37	LLB-II	24	–50	6	73	–	89
1 + 38	LL(B-a)	113	–30	39	25	70 : 30	62
1 + 38	LL(B-a)-II	113	–30	39	83	89 : 11	94
1 + 23	LL(B-a)	166	–40	25	trace	–	–
1 + 23	LL(B-a)-II	166	–40	25	84	95 : 5	95
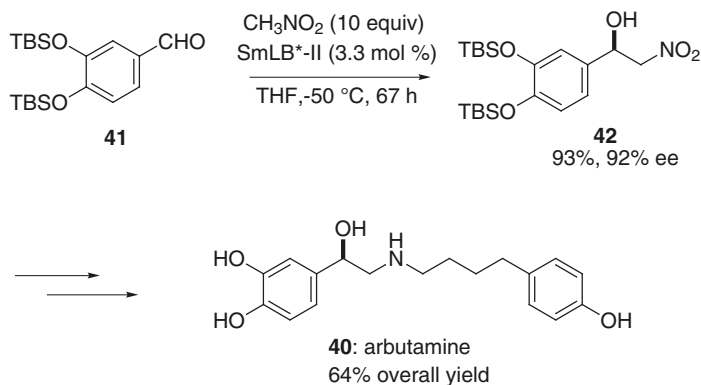
Scheme 10. A catalytic asymmetric synthesis of arbutamine. [SmLB*-II = SmLi$_3$tris(R)-6,6'-bis(trimethylsilylethynyl)binaphthoxide) + H$_2$O (1.0 mol equiv to Sm) + BuLi (0.6 mol equiv to Sm)].

utamine **40**, which is a useful β-agonist [33, 34], was achieved (Scheme 10) [8]. In the key step, the nitroaldol adduct **42** was formed in 93% yield and with 92% ee [8].

In conclusion, since the first example of a catalytic asymmetric nitroaldol reaction (Henry reaction) was reported in 1992 by Shibasaki et al., this reaction has been developed into a highly efficient synthetic method for the stereoselective synthesis of nitroalkanols. Using alkali metal-containing heterobimetallic

lanthanoid complexes as catalysts, a broad variety of nitroalkanol derivatives containing one, two, or more stereogenic centers have been constructed in a highly stereoselective manner. Until now, this new and innovative catalytic concept has been applied to the synthesis of several biologically active and pharmaceutically interesting compounds (or their precursors).

3.2
Direct Asymmetric Aldol Reaction

Although the development of a range of catalytic asymmetric aldol-type reactions has proven to be a valuable contribution to asymmetric synthesis [35–37], in all of these reactions pre-conversion of the ketone moiety to a more reactive species such as an enol silyl ether, enol methyl ether, or ketene silyl acetal has been an unavoidable necessity. However, quite recently Shibasaki et al. reported that a direct catalytic asymmetric aldol reaction, which is known in enzyme chemistry, is also possible in the presence of heterobimetallic lanthanoid catalysts [38]. Using *(R)*-LLB (20 mol%), which shows both Lewis acidity and Brønsted basicity similar to the corresponding aldolases, the desired optically active aldol adducts were obtained with up to 94% ee. A variety of aldehydes and unmodified ketones can be used as starting materials (Scheme 11).

Moreover, although it is known that aldol reactions that utilize acetone as a starting material are generally difficult to control, this reaction proceeds well in the presence of LLB (20 mol%) and 10 equiv of acetone to give the aldol adduct with up to 74% ee and in 82% yield. The postulated mechanism of this direct catalytic aldol reaction is presented in Scheme 12.

Therein, the lanthanum center ion (III) should function as a Lewis acid activating the aldehyde, whereas the lithium binaphthoxide moiety act as Brønsted base moiety. The synergetic effect of both groups, as can be seen in intermediate III, appeared to be responsible that the reaction proceeds without any activation of the starting materials, especially the ketone component.

3.3
Michael Addition Reaction

Catalytic asymmetric Michael reactions are one of the most important synthetic methods for obtaining asymmetric centers by enantioselective construction of carbon-carbon bonds [39, 40]. The first lanthanoid complex catalyzed Michael
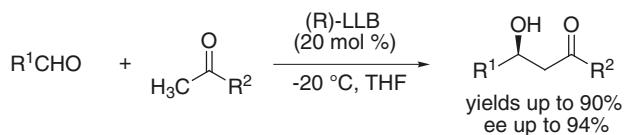
Scheme 11. LLB-catalyzed direct aldol reaction.
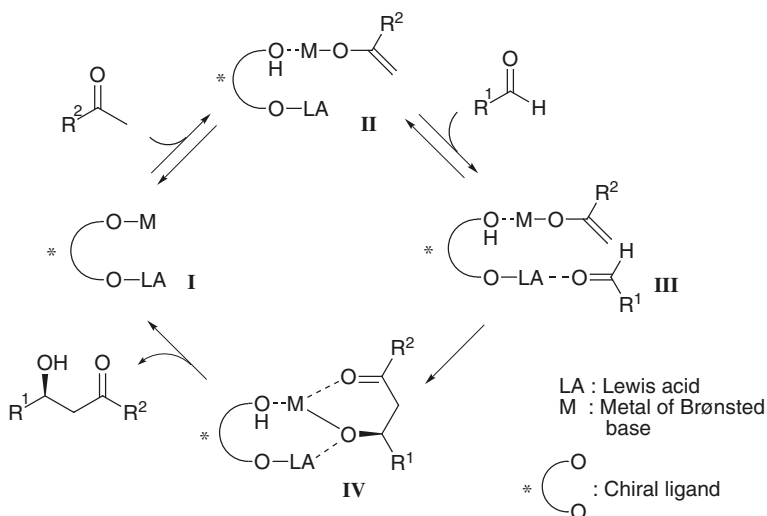
Scheme 12. Catalytic Cycle of Direct Catalytic Asymmetric Aldol Reactions.
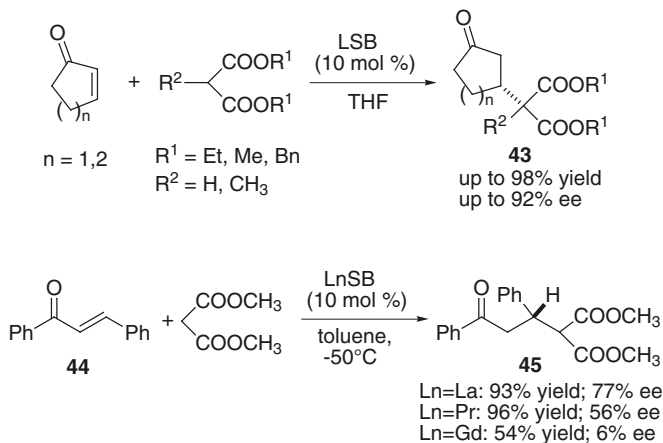
Scheme 13. LnSB-catalyzed asymmetric Michael addition.

addition reaction was realized using malonates as Michael donor in the catalytic asymmetric Michael reaction of various enones [41, 42]. Although ineffective as an asymmetric catalyst for nitroaldol reactions, LSB (L=lanthanum, S=sodium) was found to be effective in this case, giving Michael adducts **43** in up to 92% ee and almost quantitative yield (Scheme 13) [41]. In general, the use of THF as a solvent led to the best results, whereas in the case of the corresponding LSB-catalyzed reaction of *trans*-chalcone **44** the use of toluene was essential to give the product in good enantiomeric excess. Center metal effects were also investigated

for this Michael reaction, indicating that LSB was the best catalyst for catalytic asymmetric Michael reactions.

In order to clarify the nature of the interaction between the enone and the asymmetric catalyst, the complexation was studied by ^{1}H-NMR spectroscopy after mixing cyclohexenone and the asymmetric bimetallic complexes and observing the chemical shift of the α-proton of cyclohexenone [41]. Interestingly, it was found that complexation with LSB induced a small downfield shift on the α-proton of cyclohexenone whereas PrSB, a moderately effective asymmetric catalyst for Michael reactions, induced a large upfield shift. In strong contrast, in the case of either EuSB or LLB, which gave only near-racemic Michael adducts, the ^{1}H-NMR spectra showed no changes in chemical shift of the α-proton of cyclohexenone. These NMR studies indicated that the carbonyl group of the enone coordinated to lanthanum and/or praseodymium metal in the LnSB molecule, while the enone did not coordinate to either LLB and/or EuSB. These changes of chemical shift were observed even in the presence of dimethyl malonate. The chemical phenomena described above might be understood by considering the differing dihedral angles of binding of the BINOL moiety to the center metal in each case.

Additionally, computational simulations of the enantioselection process using Rappé's universal force field (UFF) [43–45] were carried out which clearly indicated that the *(R)*-LSB complex complexes better as a pro-*(R)* adduct than as pro-*(S)* adduct (ΔE=4.9 kcal/mol) [41]. The proposed catalytic cycle is shown in Scheme 14. Thus, the basic LSB complex also acts as a Lewis acid, controlling the orientation of the carbonyl function and so activating the enone to attack. It ap-
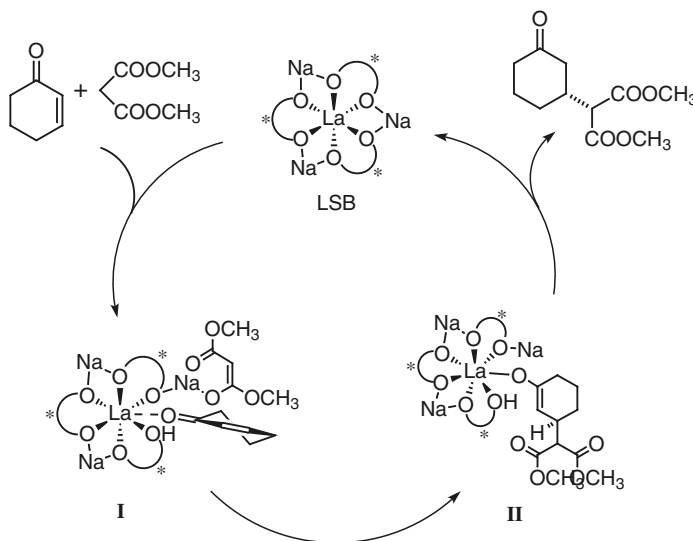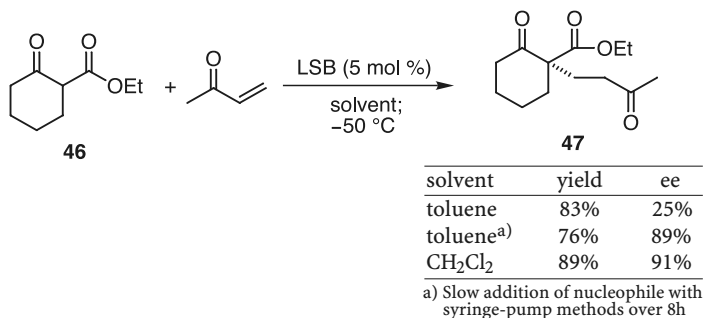

Scheme 14. Proposed catalytic cycle for the asymmetric Michael reaction promoted by LSB.

pears that the multifunctional nature of the LSB catalyst makes possible the formation of Michael adducts with high ees even at room temperature. As final step the resultant sodium enolates **II** of the optically active Michael adducts appear to abstract a proton from an acidic OH so as to regenerate the LSB catalyst. In both catalytic asymmetric Michael reactions and nitroaldol reactions, enones and/or aldehydes appear to coordinate to the rare earth metal. The reason why LSB is more effective for catalytic asymmetric Michael reactions whereas LLB is more effective for catalytic asymmetric nitroaldol reactions is still unclear at present. However, it seems that slight differences in bond lengths in chelate structures such as **I** and **II**, as well as slight differences in "bite" angle for the BINOL moiety caused by varying the alkali metal component may be responsible for this effect.

Another type of an LSB catalyzed asymmetric Michael reaction, in which the asymmetric center is induced on the side of the adduct originating from the Michael donor, was also reported by Shibasaki et al. (Scheme 15) [46]. In a preliminary study, it was found that the reaction of **46** with 3-buten-2-one in THF using 10 mol% of LSB gave **47** with 23% ee, while carrying out the reaction in toluene afforded **47** with 75% ee. However, when the amount of LSB was reduced to 5 mol%, the enantiomeric excess of **47** declined to a more modest 25% ee. To offset this decline while still maintaining the lower level of catalyst slow addition of **46** was essential. Accordingly, the use of syringe pump methods gave **47** with high enantiomeric excess (89% ee). The reaction was further improved when using CH_2Cl_2 as a solvent. Thus, the asymmetric Michael reaction catalyzed by 5 mol% of LSB in CH_2Cl_2 gave **47** in 89% yield and with 91% ee, without the need for slow addition previously encountered (Scheme 15). In addition, in this case the catalytic asymmetric Michael reaction for **47** was not so affected by the choice of rare earth metal.

In conclusion, as shown in Scheme 15, slow addition of β-keto ester and the use of CH_2Cl_2 as solvent are generally quite effective methods for preventing reduction of enantiomeric excess for the various Michael adducts. On the other

solvent	yield	ee
toluene	83%	25%
toluene[a]	76%	89%
CH_2Cl_2	89%	91%

a) Slow addition of nucleophile with syringe-pump methods over 8h

Scheme 15. LSB-catalyzed Michael addition of **46** with methyl vinyl ketone.

hand, malonates give the adducts with high ees regardless of the solvent used [41]. These results can be rationalized by comparison of the pKa of a β-keto ester with that of a malonate; the former is significantly more acidic than the latter. Thus, the concentration of the resulting Na-enolate can be expected to be greater in the case of the β-keto ester, and moreover this Na-enolate will react with an enone more slowly than the Na-enolate derived from a malonate. We suggest that this combination of more rapid formation and longer lifetime increases the likelihood of dissociation of the Na-enolate from the chelated ensemble, thus giving a product of lower ee. On the other hand, in less polar CH_2Cl_2 the Na-enolate would, even in this case, remain part of the ensemble, thereby affording the product with high ee (Fig. 4). Furthermore, it appears that slow addition of the β-keto ester also acts to limit undesired ligand exchange between BINOL moieties and the Michael donor.

In both types of catalytic asymmetric Michael reactions, the use of either second-generation LSB or 6,6'-substituted BINOL derived LSB type catalysts did not result in significantly improved results.

3.4
Diels-Alder Reaction

A further application of the heterobimetallic lanthanoid catalysts of the LLB type to the field of catalytic asymmetric Diels-Alder reactions [47, 48] was also achieved by Shibasaki et al. [49]. In general, LLB type complexes are multifunctional asymmetric catalysts, showing both Brønsted basicity and Lewis acidity. Nevertheless, in this study the use of LLB type catalysts acting as asymmetric Lewis acids alone was examined and led to the development of an LLB (type) catalyzed asymmetric Diels-Alder reaction [49]. Representative results for the catalytic asymmetric Diels-Alder reactions using **48** and cyclopentadiene in toluene as a solvent are shown in Scheme 16.
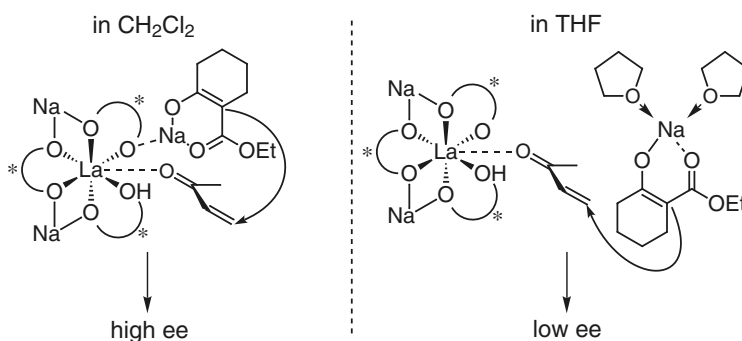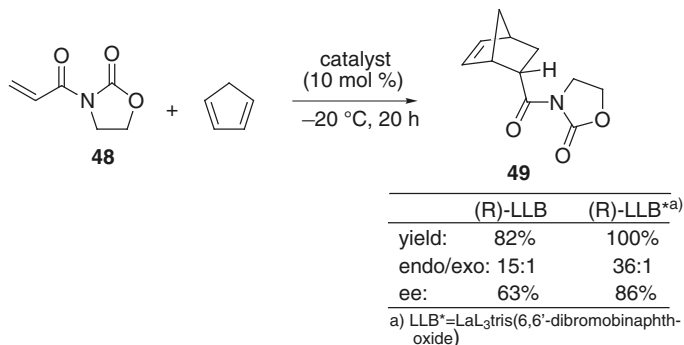

Figure 4. Proposed mechanism for the catalytic asymmetric Michael reaction promoted by LSB.

	(R)-LLB	(R)-LLB*[a]
yield:	82%	100%
endo/exo:	15:1	36:1
ee:	63%	86%

a) LLB*=LaL₃tris(6,6'-dibromobinaphth-oxide)

Scheme 16. Catalytic asymmetric Diels-Alder reaction.

Compared to the result with LLB, the use of a 6,6'-dibromosubstituted BINOL derived LLB type catalyst LLB* led to significantly improved yield, *endo:exo* ratio and enantioselectivity (86% ee). Interestingly, the addition of 12-crown-4 to the reaction medium resulted in the formation of the adduct **49** with much lower enantiomeric excess. This result appears to suggest that the lithium cation(s) play a key role in activation of the dienophile.

4
Catalytic Asymmetric C-O Bond Formation Using Heterobimetallic Lanthanoid Complexes: Epoxidation

Catalytic asymmetric epoxidations are one of the most important asymmetric processes [1]. In addition to previous successful achievements of other groups with allylic alcohols [50, 51] and unfunctionalized olefins [52–55], the first efficient catalytic asymmetric epoxidation of a variety of enones with broad generality has been developed when using chiral lanthanoid complexes [56].

In the presence of the sodium-containing heterobimetallic catalyst *(R)*-LSB (10 mol%), the reaction of enone **52** with TBHP (2 equiv) was found to give the desired epoxide with 83% ee and in 92% yield [56]. Unfortunately LSB as well as other bimetallic catalysts were not useful for many other enones. Interestingly, in marked contrast to LSB an alkali metal free lanthanoid BINOL complex, which was prepared from Ln(O-*i*-Pr)$_3$ and *(R)*-BINOL or a derivative thereof (1 or 1.25 molar equiv) in the presence of MS 4A (Scheme 17), was found to be applicable to a range of enone substrates. Regarding enones with an aryl-substituent in the α-keto position, the most effective catalytic system was revealed when using a lanthanum-*(R)*-3-hydroxymethyl-BINOL complex La-**51** (1–5 mol%) and cumene hydroperoxide (CMHP) as oxidant. The asymmetric epoxidation proceeded with excellent enantioselectivities (ees between 85 and 94%) and yields up to 95%.
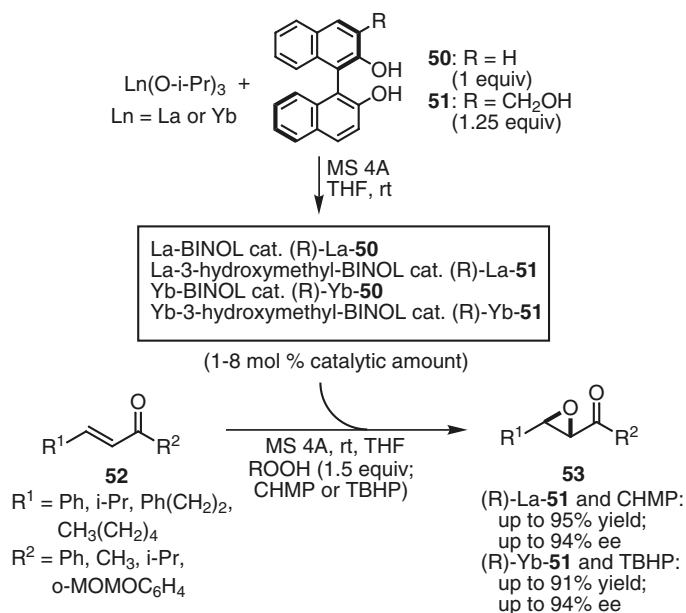
Scheme 17. Catalytic asymmetric epoxidation of enones.

In contrast to this result, the enones with an alkyl moiety in the α-keto position were best converted to the corresponding epoxides when replacing lanthanum by ytterbium in the corresponding catalytically active complex of the above mentioned type. Using TBHP (1.5 equiv) as oxidant in the presence of 5 mol% of Yb-**51** gave enantioselectivities up to 94%. However, the use of either Yb-**50** catalyst or a La-CMHP system afforded the product of type **53** with less satisfactory results. It seems likely that the difference in ionic radius between lanthanum and ytterbium, as well as the difference in Lewis acidities, accounts for the observed center metal effects.

Although the structure of the catalytically active species could not have been unequivocally determined, it was found that an almost 1:1 ratio of Ln(O-i-Pr)$_3$ (Ln=La or Yb) and BINOL gave the maximum enantiomeric excesses. In addition, an asymmetric amplification of the catalytic asymmetric epoxidation has been obtained (Fig. 5) [56], which led to the conclusion that an oligomeric structure of these lanthanoid-BINOL catalysts may play a key role in these catalytic asymmetric epoxidations of enones. Regarding the mechanism, a Ln-alkoxide moiety in the catalysts appears to act as a Brønsted base, activating a hydroperoxide moiety so as to make possible a Michael reaction. At the same time another Ln metal ion seems to act as a Lewis acid, both activating and controlling the orientation of the enone. Furthermore, it is noteworthy that this catalytic asymmetric epoxidation can be carried out at room temperature using 1–8 mol% of an asymmetric catalyst to give epoxides with good enantiomeric excesses.
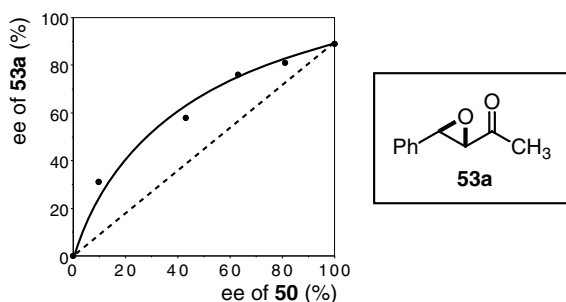
Figure 5. Asymmetric amplification in the Yb-**50** catalyzed epoxidation reaction to **50a**.

5
Catalytic Asymmetric C-P Bond Formation Using Heterobimetallic Lanthanoid Complexes

The application of the heterobimetallic lanthanoid complexes of the LnMB type led to a breakthrough in establishing a highly efficient asymmetric catalytic route to α-hydroxy as well as α-amino phosphonic acid esters, which have attracted much attention due to their wide ranging biological activity [57–64]. The heterobimetallic catalysis described below represents the first and until now the only highly efficient asymmetric catalytic approach to both α-hydroxy and α-amino phosphonates by the attractive way of asymmetric catalytic hydrophosphonylation.

5.1
Hydrophosphonylation of Aldehydes

For the first time an LLB catalyzed enantioselective hydrophosphonylation of aldehydes has been independently reported by Shibuya et al. and Rath and Spilling in the early 1990s [65, 66]. Due to the unknown catalyst structure of LLB at this time, and to the fact that the purity of LLB catalyst utilized by this groups appeared to be rather low, only low to modest ees have been achieved using LLB. According to Shibuya et al. and Rath and Spilling, the hydrophosphonylation of benzaldehyde gave the corresponding α-hydroxy phosphonates in less than 30% ee [65, 66]. However, under similar conditions Shibasaki et al.'s reinvestigation of the catalytic asymmetric hydrophosphonylation of benzaldehyde and cinnamaldehyde with 1.3 equiv of dimethyl phosphite in the presence of 10 mol% of LLB gave the corresponding α-hydroxy phosphonates in strongly improved 76% ee (79% yield) and in 72% ee (78% yield), respectively [67]. It is noteworthy that with slow addition of the aldehydes, the enantiomeric excesses of both products rose up to 83% ee (73% yield) and 79% ee (88% yield) respectively.

The reaction strongly depends on the solvent, increasing the ee from 4 to 16 to 79% ee when changing the solvent from diethyl ether to dichloromethane to THF, which has been shown to be the solvent of choice. The LLB catalyzed hydrophosphonylation was most efficient in the case of aromatic aldehydes of low reactivity or arylated α,β-unsaturated aldehydes as starting materials, with enantioselectivities in the range of 84–95% ee (Scheme 18). A comparison of the catalytic ability of LLB with its relative aluminum complex ALB showed that LLB is superior for most of the aldehyde systems. Interestingly, however, for electron-deficient aromatic aldehydes the aluminum-lithium-complex ALB gave better results (e.g. in the case of *p*-nitrobenzaldehyde: 36% ee vs 71% ee). Thus, LLB and ALB can be used in a complementary manner for the catalytic asymmetric hydrophosphonylation of aldehydes. In contrast to other reactions, herein the use of neither 6,6'-bis((triethylsilyl)ethynyl)BINOL nor the second-generation LLB catalyst gave a significant improvement in the results.

The above-mentioned effects of slow addition of the aldehydes on the enantioselection can be best explained as follows. Heterobimetallic catalysts such as LLB are believed to activate both nucleophiles and electrophiles. For the hydrophosphonylation of comparatively unreactive aldehydes the activated phosphite can react only with aldehydes which are pre-coordinated to lanthanum. However, in the case of reactive aldehydes such as benzaldehyde and cinnamaldehyde, the Li-activated phosphite may be able to undergo a competing reaction with the unactivated aldehyde. If such aldehydes are added in one portion, the ee of the product will be reduced. Slow addition of aldehyde, in contrast, has the effect of maximizing the ratio of activated to unactivated aldehyde present in solution, by allowing time for the catalytic cycle to complete and regenerate the catalyst, thereby facilitating aldehyde activation. Reactive aldehydes should, therefore, be added slowly in order to avoid the side reaction which proceeds without activation of the aldehyde by LLB (Scheme 19).

A detailed investigation into the hydrophosphonylation of substituted benzaldehydes as well as heteroaromatic aldehydes has been recently reported by Shibuya et al. [68] Therein this group found an interesting effect of the *p*-substituent on enantioselectivity. In agreement with the results reported by Shibasaki
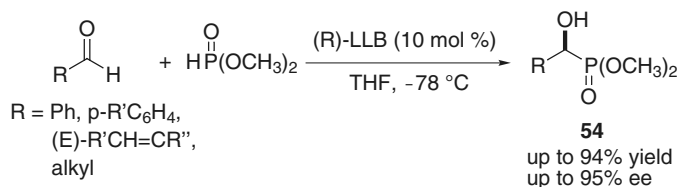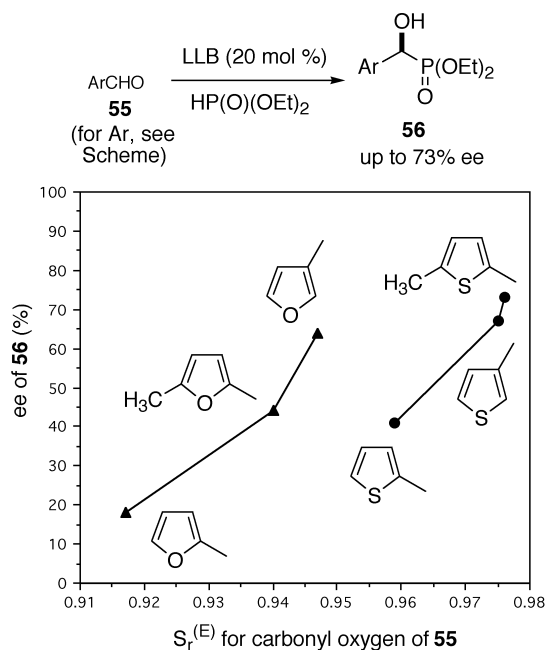

Scheme 18. LLB-catalyzed asymmetric hydrophosphonylation of aldehydes.
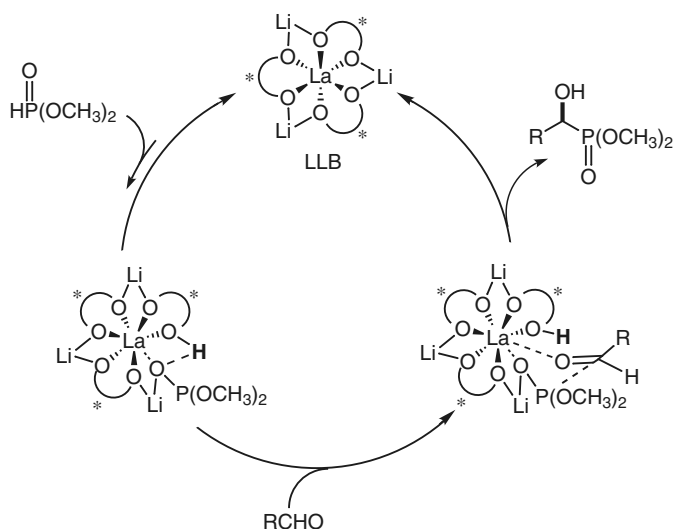
Scheme 19. A proposed catalytic cycle for asymmetric hydrophosphonylation.

et al. [67], good results were obtained when using *p*-methoxybenzaldehyde in the presence of LLB with up to 82% ee and excellent yields [68]. A significant influence of the lanthanoid metal center ion and the alkali metal component was also found, underlining that the choice of the rare earth metal and alkali metal component in the Shibasaki catalyst is a crucial factor in inducing good enantioselectivity. Interestingly, compared to LLB the use of either EuLB or SmLB as asymmetric catalyst gave the reverse enantioselection (in case of *p*-methoxy benzaldehyde), although with low ee (8 and 9%, respectively).

The role of the aromatic ring within a substrate was investigated in the LLB-catalyzed hydrophosphonylation of a range of heteroaromatic aldehydes **55** (X= O,S) with diethyl phosphite. Good yields were obtained for all products **56**, although enantioselectivities strongly varied from 18 to 73% ee (Scheme 20). The enantioselectivities obtained from the reactions with aldehydes bearing a thiophene nucleus were found to be higher than those of the corresponding furancarboxaldehyde derivatives. Regarding the series of reactions with aldehydes which possess the same heterocycle, the numerical value of the ee of the products increased with an increase in the numerical value of the super-delocalizability $S_r^{(E)}$ [69, 70] at the carbonyl oxygen within the substrates (see Scheme 20). These results reveal that the electrophilic coordination of the lanthanum atom in a presumed LLB-phosphite complex to the carbonyl atom of the aldehyde might be one critical factor governing the enantioselectivity.

Scheme for reaction:

ArCHO **55** (for Ar, see Scheme) + HP(O)(OEt)$_2$ → with LLB (20 mol %) → Ar–CH(OH)–P(O)(OEt)$_2$ **56** up to 73% ee

Graph: ee of **56** (%) versus $S_r^{(E)}$ for carbonyl oxygen of **55**

Scheme 20. LLB-catalyzed asymmetric hydrophosphonylation of heteroaromatic aldehydes.

5.2
Hydrophosphonylation of Imines

5.2.1
Hydrophosphonylation of Acyclic Imines

α-Amino phosphonic acids are interesting compounds for the use in the design of enzyme inhibitors [59, 60]. As in the case of α-hydroxy phosphonic acids, the absolute configuration of the α-carbon strongly influences the biological properties. Although several (especially diastereoselective) methods for the synthesis of optically active α-amino phosphonic acids have been known for a long time [71, 72], the first catalytic asymmetric hydrophosphonylation of imines has been reported recently by Shibasaki et al. [73] using potassium-containing LnK$_3$tris(binaphthoxide) complexes (LnPB) as most efficient catalysts.

Interestingly, almost the first results in asymmetric hydrophosphonylation with acyclic imines revealed that the lanthanum-potassium-BINOL catalyst LPB was more effective than the analog sodium and lithium complexes LSB and LLB, both of which have been shown to be highly efficient in asymmetric C-C bond formations (see Sect. 3). As a representative example, in the presence of LPB (20 mol%) and 5 equiv of dimethyl phosphite the hydrophosphonylation of im-

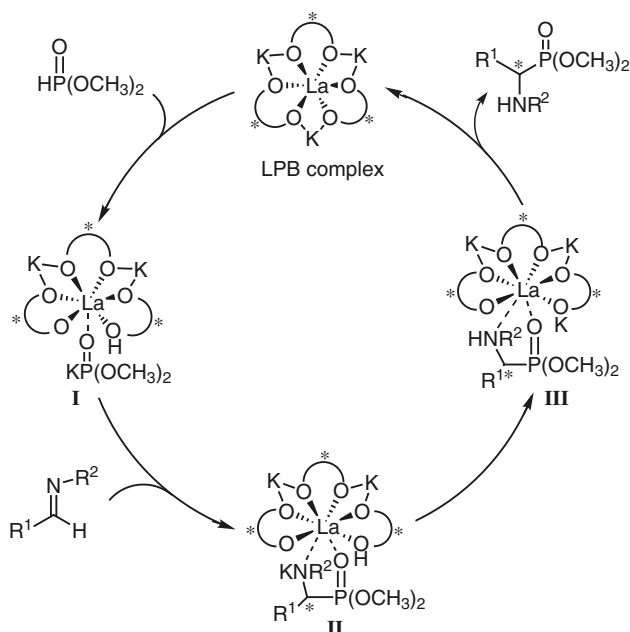ine **57a** proceeds at room temperature under formation of the desired product in 91% ee, whereas the use of LLB and LSB gave decreased enantioselectivities (LSB: 49% ee; LLB: 38% ee) and yields. Moreover, attempts to improve the efficiency of this asymmetric catalysis were successful. In the presence of only 5 or 10 mol% catalytic amount of LPB and 1.5 equiv of phosphite, another α-amino phosphonate (bearing a benzhydryl group as *N*-substituent) was obtained in excellent 92 or 96% ee and good yields up to 82% when using **57b** as imine component (Scheme 21).

The broad generality of this asymmetric hydrophosphonylation method using catalytic amounts of LPB was shown by the effective conversion of several types of imines to the corresponding optically active α-amino phosphonates in satisfactory to excellent enantioselectivities up to 96% ee and yields up to 87%. Concerning the substitution pattern of the imine component, the authors focused on the use of alkyl and alkenyl groups as C-substituents, whereas the benzhydryl group was used as *N*-substituent in most of the cases due to the possibility to cleave this group from the products in order to obtain the pure α-amino phosphonic acids with a primary amino function. In case of two imines, the use of GdPB or PrPB gave the best results. Once again, these results confirm impressively the ability of the LnMB type catalysts as a flexible asymmetric catalytic system which can be easily modified and "designed" according to the needs for the desired reaction by changing lanthanoid center ion, alkali metal component and/or BINOL derivative. However, in this reaction neither the use of second-generation LPB catalyst nor of LPB derivatives derived from modified BINOLs gave improved results.

The proposed mechanism of this catalytic asymmetric hydrophosphonylation is shown in Scheme 22. The first step of this reaction is the deprotonation of dimethyl phosphite by LPB to generate the potassium dimethyl phosphite. This potassium phosphite immediately coordinates to a rare earth to give **I** due to the strong oxophilicity of rare earth metals [74]. **I** then reacts with an imine to give an optically active potassium salt of the α-amino phosphonate, which leads via proton-exchange reaction to an α-amino phosphonate and LPB, thereby completing the catalytic cycle and giving the desired asymmetric hydrophosphonylation.

57
a: R = CH(p-CH$_3$OC$_6$H$_4$)$_2$
b: R = CHPh$_2$

58
up to 82% yield
up to 96% ee
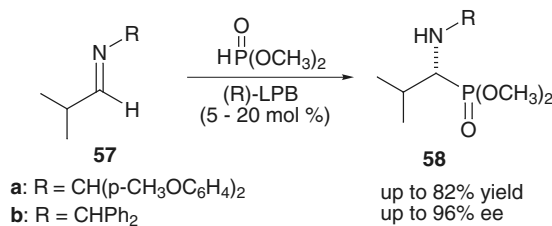
Scheme 21. Asymmetric hydrophosphonylation of acyclic imines catalyzed by (*R*)-LnPB.

HP(OCH$_3$)$_2$

K—O   O—K
O····La◄O
O O
K
LPB complex

R^1 P(OCH$_3$)$_2$
HNR^2

K—O   O—K
O···La O
O O
H
KP(OCH$_3$)$_2$
I

K   O—K
O La O
HNR^2 O K
R^{1*} P(OCH$_3$)$_2$
III

N—R^2
R^1 H

K—O   O—K
O La O
O H
KNR^2
R^{1*} P(OCH$_3$)$_2$
**II**

Scheme 22. Proposed catalytic cycle.

In conclusion, the lanthanoid complex catalyzed hydrophosphonylation of acyclic imines represents an efficient method to produce optically active α-amino phosphonates in modest to high enantiomeric excess.

5.2.2
Hydrophosphonylation of Cyclic Imines

In spite of the high level of interest in the asymmetric synthesis of α-amino phosphonic acids, less is known in the case of cyclic α-amino phosphonates. Although in recent years descriptions of promising pharmaceutical applications for cyclic compounds (and acylated derivatives thereof) have been published [61–64], until now no efficient general asymmetric route has been available to prepare this class of α-amino phosphonates. Several attempts at a diastereoselective synthetic route which were made by the addition of a stoichiometric amount of chiral phosphites to cyclic imines, namely thiazolines, gave only limited diastereoselection ratios of *dr*=2:1 or below [75, 76].

The first efficient enantioselective synthetic route to cyclic α-amino phosphonates, namely the pharmaceutically interesting heterocyclic phosphonates of type **1** [63, 64], by an asymmetric addition reaction of dialkyl phosphites to heterocyclic imines was recently developed by Shibasaki et al. (Scheme 23) [10, 77].
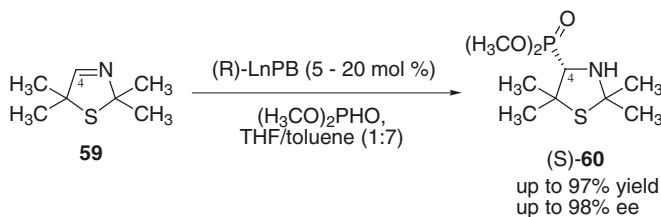
Scheme 23. Enantioselective hydrophosphonylation catalyzed by (R)-LnPB complexes.

Therein, potassium-containing heterobimetallic lanthanoid complexes have been chosen as catalysts and thiazolines of type **59** were used as the imine substrates. To produce the optically active α-amino phosphonate *(S)*-**60**, the model compound 2,2,5,5-tetramethyl-3-thiazoline **59** was treated with 5 equiv of dimethyl phosphite in the presence of several kinds of chiral lanthanoid-potassium-binaphthoxide complexes [*(R)*-LnPB]. At first, 20 mol% of LaK$_3$tris(binaphthoxide) (*(R)*-LPB) in THF/toluene (1:7) at room temperature was used, which has been shown to be the most efficient catalytic system in the asymmetric hydrophosphonylation of acyclic imines (see Sect. 5.2.1). However, only a modest enantioselectivity of 61% ee accompanied by a 53% chemical yield was observed in the formation of *(S)*-**60** using this method. The efficiency of the reaction was improved by increasing the reaction temperature to 50 °C. Investigations of the influence of further lanthanoid metal components in the catalyst structure revealed that, in the presence of Sm, Gd, Dy, and Yb, the ee values rose to 97% ee accompanied by good to high chemical yields [10, 77]. The characteristic relationship between the ionic radii of the rare earth metal ions (III) and the enantioselectivity is summarized in Fig. 6. The functional course of this graph supports the idea that *(R)*-LnMB catalysts represent a multifunctional, highly flexible catalyst system by varying their incorporated components.

In contrast to the asymmetric hydrophosphonylation of acyclic imines, the rare earth metals with lower ionic radii in the range of [Yb(III)] to [Gd(III)] were connected with the highest enantioselectivities of approximately 95% ee (whereas high optical purities with acyclic imines were achieved with La(III), a lanthanoid metal with a relatively large ionic radii). The asymmetric hydrophosphonylation of **59** with *(R)*-LPB was found to be limited, with only 64% ee. In agreement with the hydrophosphonylation of acyclic imines, potassium was needed as the alkali metal component in the complex *(R)*-LnMB to obtain acceptable results. In order to identify a highly efficient catalytic system which could maintain a high ee and yield even in the presence of small catalytic amounts, the influence of reduced catalytic amounts has been investigated. In the case of the *(R)*-SmPB catalyzed asymmetric hydrophosphonylation, a steady decrease in chemical yields was observed with smaller catalytic amounts, whereas nearly unchanged high chemical yields were obtained when reducing the concentration of the *(R)*-YbPB catalyst from 20 to 15 to 10 mol%. A further decrease in the
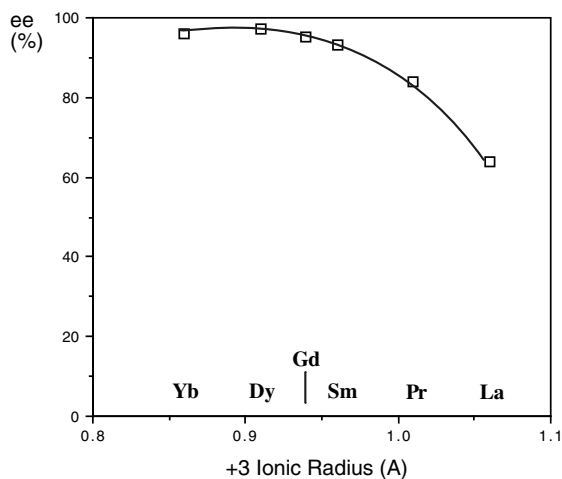
Figure 6. Effect of Lanthanoid Ionic Radii on Enantioselectivity (corresponding to the reaction shown in Scheme 23).
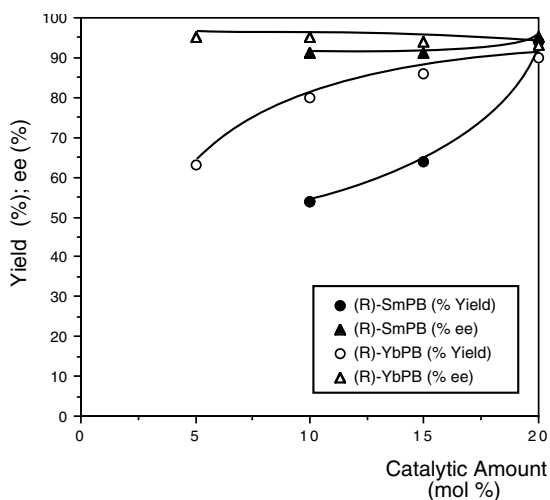
Figure 7. Influence of the catalytic amount on asymmetric hydrophosphonylation of imine **59**.

concentration of the catalyst to 5 mol% *(R)*-YbPB gave *(S)*-**60** in a still satisfactory 63% yield. In all cases the enantioselectivity of the *(R)*-YbPB-catalyzed reaction was approximately 95% ee. The functional dependence of the chemical yield and enantiomeric excess from the catalytic amount is shown schematically in Fig. 7.

Considering the superior asymmetric catalysis properties of La-Li-6,6'-disubstituted BINOL complexes in the enantioselective nitroaldol reaction, investigations were carried out with corresponding ytterbium catalysts. The use of the 6,6'-bis(methoxy)binaphthoxide derivative as ligand gave *(S)*-**60** in improved 81% chemical yield while maintaining high enantioselectivity (96% ee; catalyic amount: 5 mol%) [10]. Moreover, the flexibility of the optimized catalytic conditions with regard to other substituted thiazolines was investigated using 5 mol% catalytic amount of *(R)*-YbPB in connection with a reaction temperature of 50 ˚C and THF/toluene (1:7) as a solvent. After a 48 h reaction time all corresponding α-amino phosphonates were synthesized with high enantioselectivities (up to 96% ee) nearly independently of the substituents at the thiazoline ring system. In addition, at these reaction conditions (48 h reaction time) hydrophosphonylation of the model component **59** gave the corresponding product in further improved 88% chemical yield (compared to 63% after 40 h).

The proposed mechanistic course is shown in Scheme 24 [10]. As the first step, an interaction between the P=O bond's oxygen and the Yb(III) center ion might occur, which results in the formation of a lanthanoid/phosphite complex **I**. The preferred coordination of phosphite (instead of the theoretically also possible imine bond at the nucleophile N-atom) to Yb(III) is due to the high oxophilicity of lanthanide(III) ions. However, in structure **I** the phosphorus atom doesn't show any nucleophilic abilities, which are necessary for a nucleophilic attack on the C=N double bond. Consequently, a tautomeric rearrangement of structure **I** should take place, leading to a Ln(III)-coordinated phosphite form **IIb**. Therein, the λ^3 phosphorus atom shows enhanced nucleophilic character caused by the lone pair, which now allows a nucleophilic attack on the C=N double bond of the thiazolines. The nucleophilicity of the phosphorus atom should be further increased by (partial) deprotonation and an additional coordination of the resulting anion to the potassium in the intermediate **IIa**. Consequently, the P-nucleophile reacts (in a high enantioselective manner) with the C=N double bond of the thiazoline **59** to form the chiral potassium salt of the 4-thiazolidinyl-phosphonate **III**. A subsequent proton-exchange reaction step produces the α-amino phosphonate *(S)*-**60** and *(R)*-LnPB, which are connected to each other in structure **IV**. The final step of the catalytic cycle is achieved by a dissociation of the α-amino phosphonate *(S)*-**60** from the rare earth complex **IV**, which regenerates the "free" catalyst *(R)*-LnPB.

As shown in Fig. 8, two possibilities are conceivable for the addition step of the imine to the lanthanoid-phosphite complex **IIa**. To determine whether structure **V** or **VI** seems to be the more reasonable in the addition reaction of a dimethyl phosphite with the C=N double bond of cyclic imines, several hydrophosphonylation experiments using different types of phosphites were carried out in the presence or absence of the Lewis acid boron trifluoride. As it was shown that a high level of Lewis acid activation of the imine is required independently from the nucleophilicity of the phosphorus nucleophile which was used, a transition state of type **VI** appeared to exist as the dominant transition state structure.
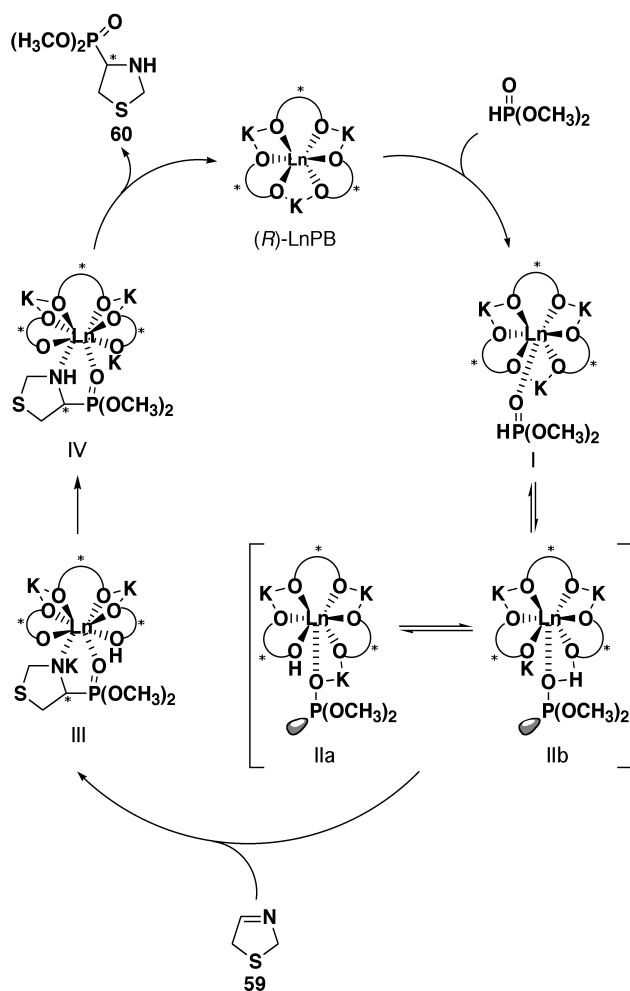
Scheme 24. Proposed reaction mechanism (for graphical reasons, the substituents at the thiazoline **59** are not shown in this scheme).
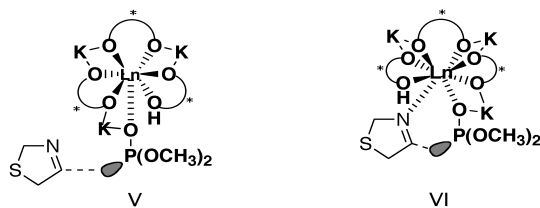

Figure 8. Two possibilities for coordination of imine in the addition step.

6
Summary

In conclusion, chiral heterobimetallic lanthanoid compexes LnMB, which were recently developed by Shibasaki et al., are highly efficient catalysts in stereoselective synthesis. This new and innovative type of chiral catalyst contains a Lewis acid as well as a Brønsted base moiety and shows a similar mechanistic effect as observed in enzyme chemistry. A broad variety of asymmetric transformations were carried out using this catalysts, including asymmetric C-C bond formations like the nitroaldol reaction, direct aldol reaction, Michael addition and Diels-Alder reaction, as well as C-O bond formations (epoxidation of enones). Thereupon, asymmetric C-P bond formation can also be realized as has been successfully shown in case of the asymmetric hydrophosphonylation of aldehydes and imines. It is noteworthy that all above-mentioned reactions proceed with high stereoselectivity, resulting in the formation of the desired optically active products in high to excellent optical purity.

7
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Reactions of Ketones with Low-Valent Lanthanides: Isolation and Reactivity of Lanthanide Ketyl and Ketone Dianion Complexes

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Recent progress in the chemistry of structurally well-defined lanthanide ketyl and ketone dianion complexes is reviewed, with particular emphasis on the ligand effects on the reactivity of these complexes. It has been demonstrated that the stability and reactivity of the ketyl radical and ketone dianion species strongly depend on the steric and electronic properties of the ancillary ligands, the structure of their parent ketones, as well as the nature of the metals to which they are bound. Fine-tuning these factors can control the reactivity of these species. Generation and reactions of dianionic thioketone and imine species are also briefly described.

Keywords: Ketyl radicals, Ketone dianions, Lanthanides, pinacol coupling, Ligand effects

1
Introduction

Reactions of ketones with low-valent lanthanides such as SmI_2 and the Ln (Ln= Sm, Yb) metals constitute one of the most useful reactions in lanthanide-mediated organic synthesis, and occupy an important position in modern organic chemistry [1, 2]. It is well known that one-electron reduction of ketones by low-valent lanthanides easily produces the corresponding radical anion species, or ketyls. In the case of diaryl ketones, further one-electron transfer is also achievable to afford the corresponding ketone dianions. These highly reactive species play a very important role, as key intermediates, in a variety of useful reactions involving ketones, such as reductions, ketyl-olefin couplings, pinacol couplings, intermolecular cross couplings, and the Barbier-type reactions. Although other reducing metals such as alkali, alkaline earth, and low-valent titanium metals can also produce similar ketyls or ketone dianions upon reaction with ketones [3], the lanthanide species usually behave differently from those metal analogs and in many cases show higher reactivity and chemo-, regio- and stereo-selectivity.

Despite the extensive applications and importance of the lanthanide ketyl and ketone dianion species in organic synthesis, very little was known about their structures. Our understanding about the reactivity of this important class of species had relied solely on the analysis of the organic products obtained by hydrolysis work-up of the final reaction mixtures. Attempts to isolate these species were greatly hampered by their extremely high reactivity and air and moisture sensitivity [4].

It was not until very recently that significant progress has been made in this field. By using sterically demanding ancillary ligands under an extremely dry and oxygen-free inert atmosphere, several different types of lanthanide ketyl and ketone dianion complexes have been successfully isolated and many of them structurally characterized. Detailed studies on the reactivity of these well-defined complexes have offered unprecedented insights into the mechanistic aspects of the reactions of ketones with low-valent lanthanides, and also shed new lights on similar reactions with other reducing agents. This article is intended to highlight the recent progress in this area, with particular emphasis on the structure-reactivity relation of lanthanide ketyl and ketone dianion complexes.

2
One-Electron Reduction of Ketones

The most difficult problem in isolating a ketyl species generated in one-electron reduction of ketones is due to its rapid hydrogen abstraction and/or coupling reactions. To suppress these decomposition reactions, it is essential to use sterically demanding reducing agents and highly conjugated ketones [5]. It has been found that several types of lanthanide reducing agents are able to afford isolable and structurally characterizable ketyl complexes in the reactions with benzo-

phenone and fluorenone. The structures and reactivity (stability) of the lantha-
nide ketyl complexes are strongly dependent on the ancillary ligands, solvents,
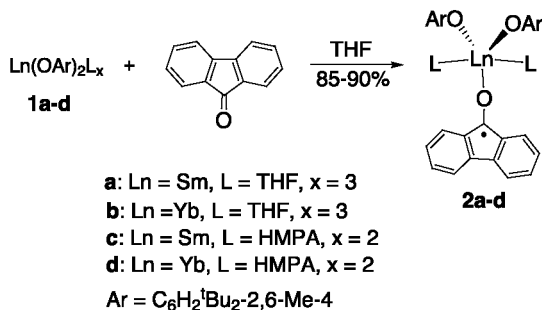and the structure of their parent ketones.

X-ray analyses have shown that the C-O bond distance of a ketyl unit is gen-
erally around 1.30 Å, which is longer than that of a free ketone (ca. 1.20 Å) and
shorter than that of an alkoxide (ca. 1.40 Å). The radical carbon atom of a ketyl
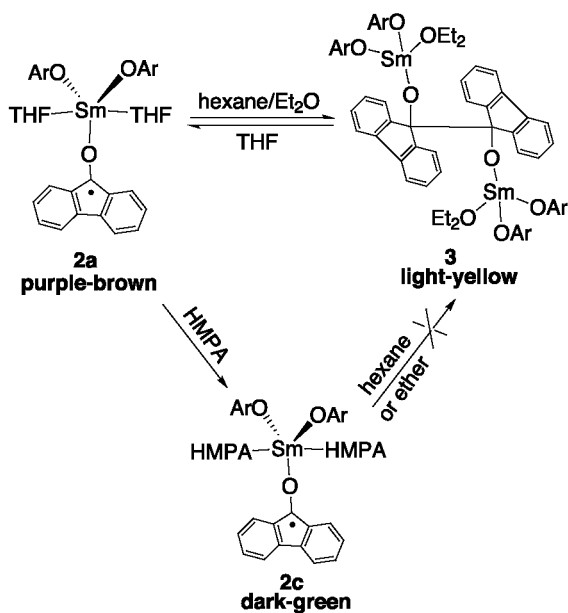is still in a sp^2-hybrid state.

2.1
Fluorenone Ketyl Complexes with an Aryloxide (ArO) Ligand

Reactions of the divalent lanthanide aryloxide complexes $Ln(OAr)_2(L)_x$ (Ar=
C_6H_2-tBu_2-2,6-Me-4; **1a**: Ln=Sm, L=THF, x=3; **1b**: Ln=Yb, L=THF, x=3; **1c**: Ln=
Sm, L=HMPA, x=2; **1d**: Ln=Yb, L=HMPA, x=2) with 1 equivalent of fluorenone
in THF at room temperature give the corresponding ketyl complexes **2a-d** as
deeply-colored crystals in high yields (Scheme 1) [6, 7]. Complexes **2a-d** all have
a similar structure in which one fluorenone ketyl and two ArO ligands are placed
at the equatorial and two L (L=THF or HMPA) ligands are located at the apical
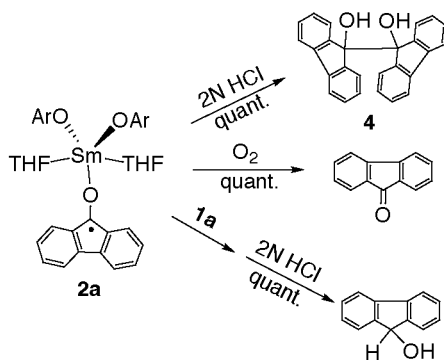positions of a distorted trigonal bipyramid.

When the THF-coordinated complex **2a** is dissolved in hexane/ether, the two
THF ligands are substituted by one molecule of OEt_2, and the ketyl radical
dimerizes into a pinacolate (**3**) (Scheme 2) [6, 7]. More remarkably, the newly
formed C-C bond in **3** (1.613(9) Å) can be easily broken to quantitatively regen-
erate the ketyl **2a** when **3** is dissolved in THF (Scheme 2), which unequivocally
demonstrates that the pinacol coupling process of the ketyl radical is completely
reversible. Addition of 2 equivalents of HMPA (per Sm) to a THF solution of **2a**
or **3** gives almost quantitatively the corresponding HMPA-coordinated ketyl
complex **2c** (Scheme 2). Since the coordination ability of HMPA is much strong-
er than that of THF [8], complex **2c** is much more stable than **2a**, and no change
was observed when **2c** was treated similarly with hexane/ether. These results
clearly demonstrate that the stability and reactivity of a ketyl species are strong-

a: Ln = Sm, L = THF, x = 3
b: Ln =Yb, L = THF, x = 3
c: Ln = Sm, L = HMPA, x = 2
d: Ln = Yb, L = HMPA, x = 2
Ar = $C_6H_2{}^tBu_2$-2,6-Me-4

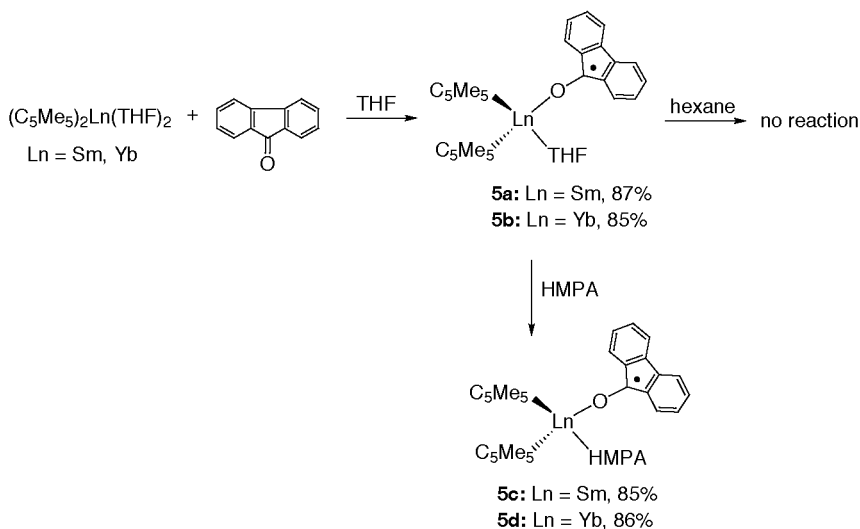**Scheme 1**

Scheme 2

Scheme 3

ly influenced by the ancillary ligands bound to the central metal, and HMPA is a better ligand than THF for the stabilization of a ketyl species [5, 7, 9].

Reflecting the typical reactivity of a ketyl species, hydrolysis of **2a** gives the corresponding pinacol-coupling product 4, while air oxidation of **2a** yields fluorenone almost quantitatively (Scheme 3). Reaction of **2a** with one equivalent of **1a** produced a THF-insoluble purple precipitate which upon hydrolysis afforded fluorenol quantitatively, suggesting that a fluorenone dianion intermediate was formed [7, 9].
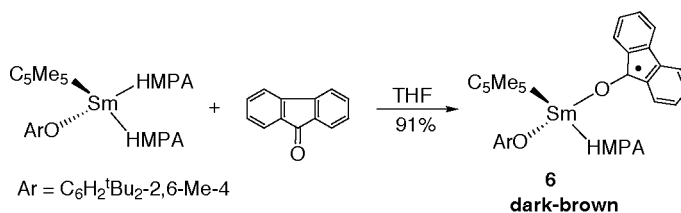
2.2
Fluorenone Ketyl Complexes with a C₅Me₅ Ligand

The similar reactions of $(C_5Me_5)_2Ln(THF)_2$ (Ln=Sm, Yb) with 1 equivalent of fluorenone in THF give the corresponding ketyl complexes **5a,b** in 85–87% isolated yields (Scheme 4) [7]. Reactions of **5a,b** with 1 equivalent of HMPA afford the HMPA-coordinated ketyl complexes **5c,d**. In contrast with the ArO-ligated ketyl complexes **2a–d** which require two THF or HMPA ligands as an additional stabilizing moiety, the C_5Me_5-ligated complexes **5a–d** need only one THF or HMPA ligand for the stabilization of the ketyl species. This difference apparently results from the larger size of C_5Me_5 as compared to that of the ArO ligand. Addition of hexane/ether to the THF-coordinated ketyl complexes **5a,b** did not cause any further reaction (Scheme 4), showing that the C_5Me_5-supported **5a,b** are more stable and less reactive than the ArO-supported **2a,b** (see also Sect. 2.1).

5a: Ln = Sm, 87%
5b: Ln = Yb, 85%

5c: Ln = Sm, 85%
5d: Ln = Yb, 86%

Scheme 4

Ar = C₆H₂ᵗBu₂-2,6-Me-4

6
dark-brown

Scheme 5

Reaction of $(C_5Me_5)Sm(OAr)(HMPA)_2$ with 1 equivalent of fluorenone in THF also gives the corresponding ketyl complex **6** (Scheme 5) [7], demonstrating that the heteroleptic C_5Me_5/OAr ligand set [10] is also able to stabilize a ketyl species. It is also noteworthy that although the homoleptic analogs **2c** and **5c** are isolable, ligand redistribution of **6** to give either of these complexes was not observed. Complex **6** represents a rare example of a lanthanide complex which bears all different ligands.

2.3
## Fluorenone Ketyl Complexes with an N(SiMe₃)₂ Ligand

The ketyl species stabilized by $N(SiMe_3)_2$ behaves a little differently from those by C_5Me_5 and the ArO ligand. Reaction of $Sm(N(SiMe_3)_2)_2(THF)_2$ with 1 equivalent of fluorenone in THF gave a brown solution whose UV-Vis spectrum was almost identical to that of the ArO-ligated ketyl complex **2a**, suggesting that the corresponding ketyl species **7a** was formed [7]. However, attempts to isolate the ketyl species **7a** from THF were unsuccessful and always resulted in the formation of the light yellow pinacolate **8a** (Scheme 6).

The central C-C bond in **8a** could also be cleaved by addition of a strongly coordinative solvent. Dissolving the light yellow **8a** in THF gave immediately a brown solution whose UV-Vis spectrum was the same as that of the solution originally obtained by the reaction of $Sm(N(SiMe_3)_2)_2(THF)_2$ with fluorenone in THF (Scheme 6). Addition of 4 equivalents of HMPA to this THF solution afforded the bis(HMPA)-coordinated ketyl complex **7b** together with the mono(HMPA)-coordinated pinacolate complex **8b** (Scheme 7) [7].

The isolation of the pinacolate **8a** rather than the ketyl **7a** from THF (Scheme 6) and the isolation of the mono(HMPA)-coordinated pinacolate **8b** together with the bis(HMPA)-coordinated ketyl **7b** in the reaction of **8a** or **7a** with HMPA (Scheme 7) contrast sharply with the similar reactions of the ArO-ligated complex **2a** or **3**, in which only the bis(THF or HMPA)-coordinated ketyl complexes were isolated (see also Sect. 2.1). These differences probably result from the difference in electron-donating ability between $N(SiMe_3)_2$ and the ArO ligand. Since $N(SiMe_3)_2$ is more electron-donating than the ArO ligand, dissociation of a neutral L (L=THF or HMPA) ligand from the central Sm atom in the
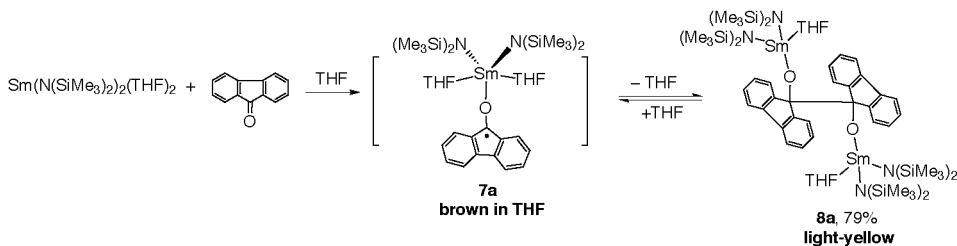
Scheme 6
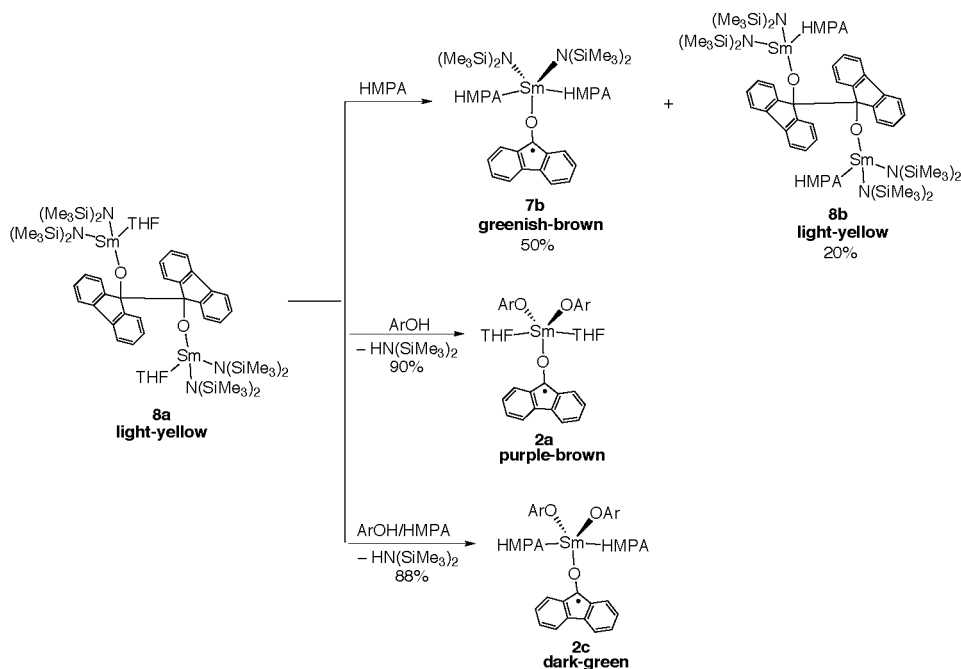
Scheme 7
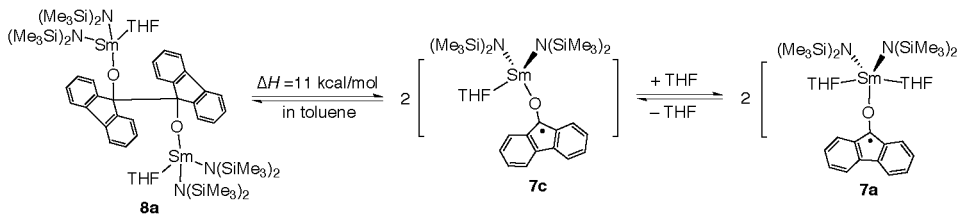
Scheme 8

(Me₃Si)₂N-ligated complexes **7a,b** would be easier than that in the ArO-ligated complexes **2a,c**, which thus causes pinacol-coupling of the ketyl radical in **7a,b** to occur more easily. In accord with this consideration, when 4 equivalents of ArOH were added to a THF solution of **8a**, the corresponding ArO-ligated ketyl complex **2a** was isolated in 90% yield with the release of HN(SiMe₃)₂ (Scheme 7). The similar reaction of **8a** with ArOH in THF/HMPA yielded selectively the corresponding bis(HMPA)-coordinated ketyl complex **2c** (Scheme 7) [7].

To gain more information concerning the C-C bond cleavage of the pinacolate **8a**, a variable-temperature UV-Vis spectroscopic study in toluene was carried out. The derived dissociation enthalpy DH_{diss} for **8a** to give **7c** is 11 kcal/mol (Scheme 8) [7]. This value is much smaller than that reported for silicon benzo-

pinacolate, $Me_3SiOC(Ph)_2C(Ph)_2OSiMe_3$ (31 kcal/mol) [11], but comparable with that reported for the C_a-C_{para} bonds in the trityl dimer $[Ph_3C]_2$ (11–12 kcal/mol) [12] and that for the dimeric titanium(IV) alkoxide/enolate complex $[(^tBu_3SiO)_3Ti(OCPh_2)]_2$ (18 kcal/mol) [13]. Obviously the dissociation enthalpy for **8a** to give the bis(THF)-coordinated ketyl complex **7a** should be much smaller than this value, since this process is accompanied by the formation of two new Sm(III)-THF bonds (Scheme 8). Since the bond energy of a Sm(II)-THF bond in $(C_5Me_5)_2Sm(THF)_n$ (n=1 or 2) is about 5–7 kcal/mol [14], and a Sm(III)-THF bond is generally stronger than a Sm(II)-THF bond, the formation of two Sm(III)-THF bonds in the course of the transformation of **8a** to **7a** would release more than 10 kcal/mol, which could well compensate the enthalpy (11 kcal/mol) for the cleavage of the central C-C bond in **8a**. It is thus not difficult to understand that when a large excess of THF is present (e.g., in THF solution), the equilibria in Scheme 8 will be greatly shifted to the right, and complete dissociation of **8a** to **7a** will be easily achieved.

2.4
Benzophenone Ketyl Complexes

Compared to the planar fluorenone ketyl, benzophenone ketyl is less conjugated and thus more reactive [15]. Reactions of benzophenone with the lanthanide reducing agents which were successfully used for the isolation of fluorenone ketyl complexes did not give a structurally characterizable benzophenone ketyl species, and in many cases yielded the corresponding hydrogen abstraction products. For example, reaction of **1d** with 1 equivalent of benzophenone in THF gave after a few weeks the colorless ytterbium(III) aryloxide/diphenylmethoxide complex $Yb(OCHPh_2)_2(OAr)(HMPA)_2$ (**9**) via hydrogen radical abstraction from solvent by the initially generated ketyl radical species (Scheme 9) [7].
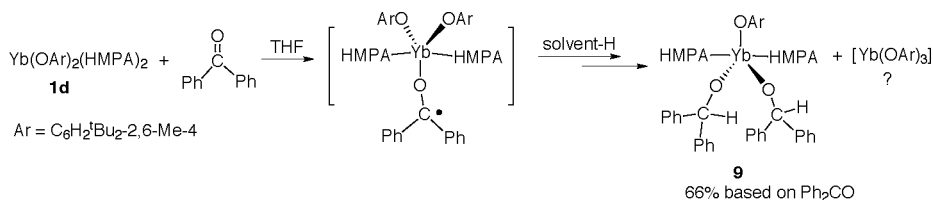
Scheme 9
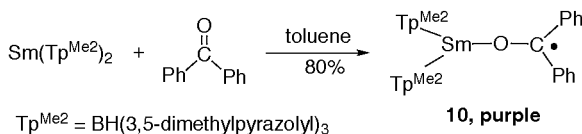
Scheme 10

Recently, Takats and coworkers have successfully isolated a structurally characterizable lanthanide benzophenone ketyl complex (**10**) by using a further sterically demanding reducing agent, $Sm(Tp^{Me2})_2$ (Tp^{Me2}=BH(3,5-dimethylpyrazolyl)$_3$) (Scheme 10) [16a]. Izod and coworkers have isolated and structurally characterized the corresponding benzophenone ketyl complex by using $Sm(C(SiMe3)_2(SiMe2OMe))_2(THF)$ as a rducing agent [16b]. These results again demonstrate that the behavior of a ketyl species is greatly influenced by the ancillary ligands.

2.5
Complexes Bearing Three Independent Ketyl Ligands

In contrast with the divalent lanthanide complexes, which are one-electron transfer agents and afford complexes consisting of one ketyl per metal ion upon reaction with ketones, the zero valent lanthanide metals are three-electron transfer agents, and their reactions with ketones, if straightforward, should yield complexes bearing three independent ketyl ligands. However, compared to mono(ketyl) complexes, the isolation of a multi(ketyl) metal species is generally more difficult and challenging, since intramolecular pinacol-coupling of ketyl radicals is also possible besides the common intermolecular reactions.

It has been found that the use of HMPA as a coordinating ligand can sufficiently suppress coupling reactions of the ketyl radicals in multi(ketyl) metal complexes to allow their isolation [5, 7, 15, 17]. Thus, reaction of Sm metal powder with 3 equivalents of fluorenone and 3 equivalents of HMPA in THF afforded the corresponding Sm(III) tris(fluorenone ketyl) complex **11a** as black-green blocks (Scheme 11) [7, 17]. An X-ray analysis has shown that this complex possesses an octahedral structure, in which the central Sm atom is coordinated in *mer*-type fashion by three ketyls and three HMPA ligands. The similar reaction of Yb metal with 3 equivalents of fluorenone gives the Yb(III) tris(ketyl) complex **11b** (Scheme 11), which is isostructural and isomorphous with **11a** [7].

Hydrolysis of **11a,b** gives almost quantitatively the corresponding pinacol **4** (Scheme 11). Interestingly, the reaction of **11a** with 0.5 equivalents of **4** yields the dimeric samarium(III) fluorenoxide/pinacolate complex **12** and fluorenone (Scheme 11) [7]. Further studies have confirmed that the formation of **12** is via hydrogen atom abstraction from the pinacol by one ketyl, followed by pinacol-coupling of the other two ketyls together with simultaneous release of two HMPA ligands in **11a** (Scheme 11). Homolytic C-C bond cleavage of the biradical species **13**, which is formed by dehydrogenation (–H·) of pinacol **4**, affords fluorenone. It is noteworthy that the small steric change, which is caused by the transformation of one of the three fluorenone ketyls to a fluorenoxy unit, has imposed crucial influence on the stability and reactivity of the other two ketyls.

In contrast with the case of fluorenone, similar reactions of Ln/HMPA (Ln= Sm, Yb) with benzophenone did not give an isolable ketyl species and yielded finally decomposition products, demonstrating again that benzophenone ketyl is more reactive than fluorenone ketyl [7]. These reactions are also in sharp con-
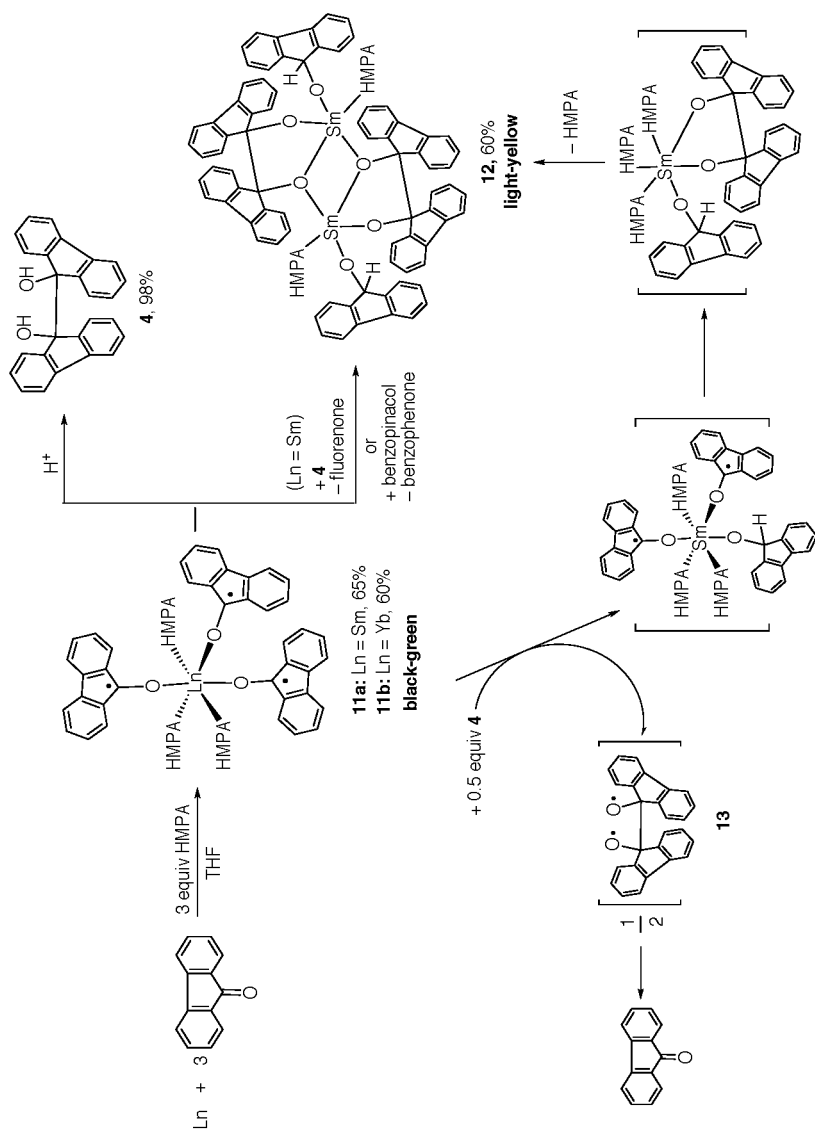
Scheme 11

trast with those of Na/HMPA [5] or Ca/HMPA [5, 15] with benzophenone, in which the corresponding benzophenone ketyl species have been successfully isolated and structurally characterized. These results show that the nature of the reducing metals also strongly influences on the reactivity and stability of a ketyl species and the lanthanide ketyl species are more reactive than those of alkali and alkaline earth metals.

2.6
Structure-Reactivity Relation of Lanthanide Ketyl Complexes

The results described above have demonstrated that the stability and reactivity of a ketyl species are extremely susceptible to the environment around the central metal ion. Both anionic and neutral (solvent) ligands play an important role in determining the behavior of a ketyl species. The sterically demanding bis(pentamethylcyclopentadienyl) ligand set $(C_5Me_5)_2$ together with a neutral L (L=THF or HMPA) ligand offers a good stabilizing environment for a lanthanide fluorenone ketyl species, while the less bulky $(ArO)_2$ or $((Me_3Si)_2N)_2$ ligand set requires two L (L=THF or HMPA) ligands for the stabilization of the same ketyl species. In the latter case, dissociation of one of the two L ligands from the central metal ion easily occurs to cause pinacol-coupling of the ketyl, and this takes place more easily for the $(Me_3Si)_2N$-ligated complexes than for the ArO-ligated ones, due to the stronger electron-donating ability of $N(SiMe_3)_2$. Re-coordination of an L ligand to the metal atom of the resulting pinacolate easily cleaves the central C-C bond and regenerates the ketyl, which thus makes the pinacol-coupling process reversible. The relatively small dissociation enthalpy for the pinacolate complexes (e.g., DH_{diss}=11 kcal/mol for **8a**) could well account for this reversibility. HMPA, as a neutral and strongly coordinating ligand, offers an excellent stabilizing moiety for both mono- and multi-ketyl complexes. The transformation of the tris(ketyl) complex **11a** to the fluorenoxide/pinacolate complex **12** provides unprecedented insights into the elementary steps of the hydrogenation and pinacol-coupling reactions of a ketyl species. Ketone-dependence of the stability of ketyls is also observed. In contrast to fluorenone ketyl complexes, the isolation of a structurally characterizable benzophenone ketyl complex is more difficult due to its less conjugated structure which makes it more reactive and less stable. However, by choosing an appropriate ligand set such as bis(hydrotris(3,5-dimethylpyrazolyl)borate), a structurally characterizable lanthanide benzophenone ketyl species can indeed be isolated. It is obvious from these results that the stability and reactivity of a ketyl radical species can be controlled through tuning the ancillary ligands bound to the central metal ion.

3
Two-Electron Reduction of Ketones

Among all low-valent lanthanides, the zero valent Sm and Yb metals are the most often used reducing agents for the study of two-electron reduction of ketones.

Although earlier studies showed that the formation of a samarium ketone dianion species was not as efficient as that of ytterbium [18–20], it was later found that samarium ketone dianion species could be generated similarly if the metal surface was sufficiently activated, e.g., by ICH_2CH_2I [21, 22]. Since the negatively charged carbon and oxygen atoms in a ketone dianion species are adjacent, the use of a sterically demanding lanthanide(II) reducing agent does not necessarily give a good result for the isolation of such species because of the steric repulsion between the resultant two closely located bulky metal moieties. Therefore, the control of the reactivity or stability of a ketone dianion species through tuning the ancillary ligands may not be as effective as in the case of ketyls. Moreover, compared to the mono-anionic ketyls, ketone dianions are more difficult to generate. They are more sensitive to air and moisture, and thus more difficult to handle. Probably due to these reasons, structurally characterized examples of ketone dianion species remain very scarce [23–25], and only one lanthanide ketone dianion complex, $[Yb(m-h^1,h^2-OCPh_2)(HMPA)_2]_2$, has been isolated and structurally characterized to date (see below) [24]. The known ketone dianions are limited solely to those bearing two aromatic groups on the carbonyl carbon atom.

Despite these limitations, it has been found that the lanthanide ketone dianions are an interesting class of species which show unique reactivities. As described below, in lanthanide ketone dianion species the carbonyl carbon atom is completely changed from electrophilic to nucleophilic, and shows strong nucleophilicity towards a variety of organic substrates. Due to the delocalization of the negative charges in the aromatic groups, some reactions can also take place at the aromatic ring.

3.1
## Isolation of an Ytterbium(II) Benzophenone Dianion Complex

Reaction of Yb metal powder with 1 equivalent of benzophenone in THF/HMPA gives the Yb(II) benzophenone dianion complex $[Yb(m-h^1,h^2-OCPh_2)(HMPA_2)]_2$ (14) as purple crystals (Scheme 12) [21, 24]. X-ray analysis has revealed that complex 14 possesses a dimeric structure, in which the two Yb atoms are bridged by two benzophenone dianions. The bridge is built in such a manner

14, purple
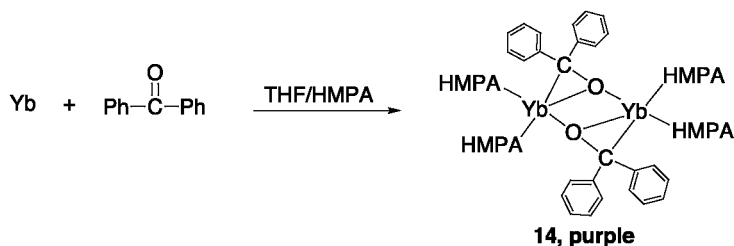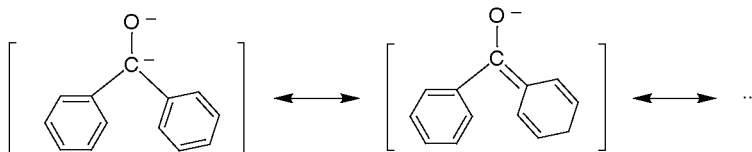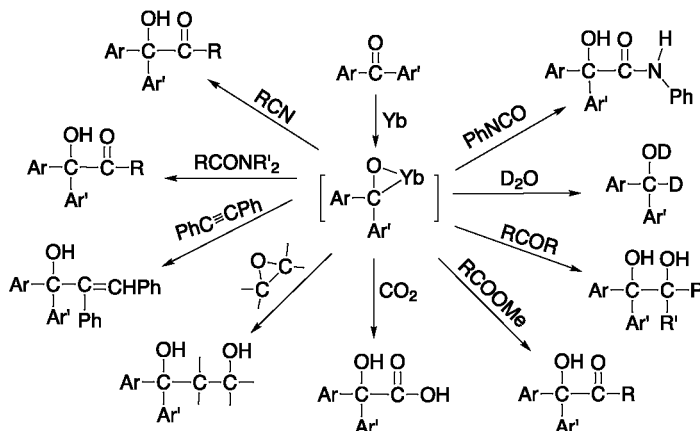
Scheme 12

Scheme 13

Scheme 14

that a benzophenone dianion uses its O atom to make a Yb-O bond with one Yb(II) ion and its C atom to make a Yb-C bond with the other Yb(II) ion to which the lone electron pair of the oxygen atom is also donated (Scheme 12). The C-O bond of the benzophenone dianion (1.39(6) Å) is longer than that of benzophenone ketyl (1.31(2) Å) [15, 16] and that of free benzophenone (1.23(1) Å) [26]. Similar to benzophenone ketyl, the carbonyl carbon atom in benzophenone dianion is still in an sp^2-hybrid state, which can thus allow good conjugation of the negative charges with the phenyl rings.

Consistent with the above structural observations, the ^{1}H NMR signals for the phenyl groups in 14 in THF-d_8 are greatly upfield shifted to as high as d 5.63–7.04, demonstrating that the negative charges of the ketone dianion are indeed highly delocalized into the phenyl rings, especially to the para-positions (d 5.63) (Scheme 13) [21,22]. As described in Sect. 3.3, this delocalization of electrons can have great influence on the reactivity of benzophenone dianion species.

3.2
Reactions of Ketone Dianions with Organic Electrophiles

It has been found that lanthanide ketone dianion species are excellent nucleophiles, which react smoothly with a variety of organic substrates such as ke-

tones, nitriles, epoxides, CO_2, etc. to give after hydrolysis the corresponding unsymmetrical pinacols, a-hydroxy ketones, 1,3-diols, a-hydroxy carboxylic acids, etc., in good yields, respectively (Scheme 14) [18–20]. Compared to alkali metal ketone dianions, they are less basic and more nucleophilic, and selectively undergo addition reactions even with substrates bearing active a-protons, such as aliphatic ketones and nitriles.

3.3
Reactions of Ketone Dianions with 2,6-Di-*tert*-Butylphenols

Most of the reactions of ketone dianion species, including those of main group and titanium metals, are known to occur at the carbonyl unit, as demonstrated in Sect. 3.2. However, it was found that the protonation reactions of lanthanide benzophenone dianion species with 2,6-di-*tert*-butylphenols can take place not only at the carbonyl group but also at the phenyl ring, due to the delocalization of the negative charges onto the aromatic groups. The selectivity between reactions at the carbonyl group and those at the aromatic ring in lanthanide diaryl ketone dianion species depends greatly on the nature of both metals and ketones.

3.3.1
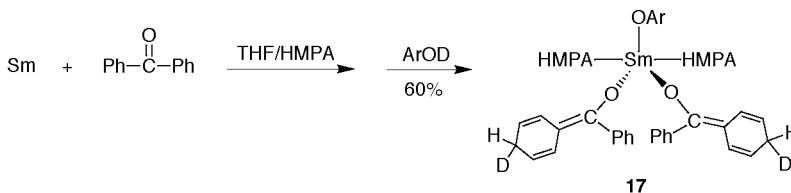### *Benzophenone Dianion Species*

Reaction of the Yb(II)-benzophenone dianion complex **14** with ArOH (Ar= C_6H_2-*t*Bu_2-2,6-R-4, R=H, Me) gave the corresponding ytterbium(II) bis(aryloxide) complex Yb(OAr)$_2$(HMPA)$_2$ (**1d**) as a major product, which was formed by the protonation of both the carbon and oxygen atoms of the carbonyl unit with ArOH (Scheme 15) [22, 24]. Besides **1d**, an ytterbium(III) enolate complex (**15**) was also obtained as a minor product. In contrast, when the analogous Sm(II) benzophenone dianion species was allowed to react with ArOH, the samarium(III) enolate complex **16**, which is analogous to **15**, was formed as a major product, while the samarium(II) bis(aryloxide) complex Sm(OAr)$_2$(HMPA)$_2$, an analog of **1d**, was not observed (Scheme 16) [22, 27]. The similar reaction of the Sm(II) benzophenone dianion species with ArOD yielded the corresponding
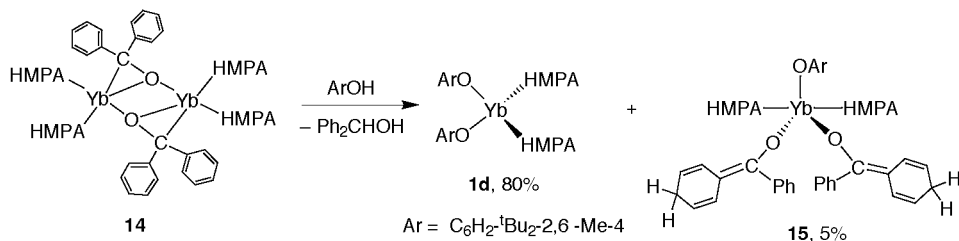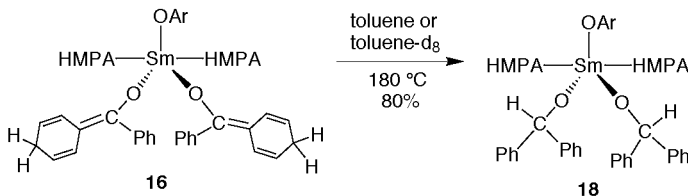

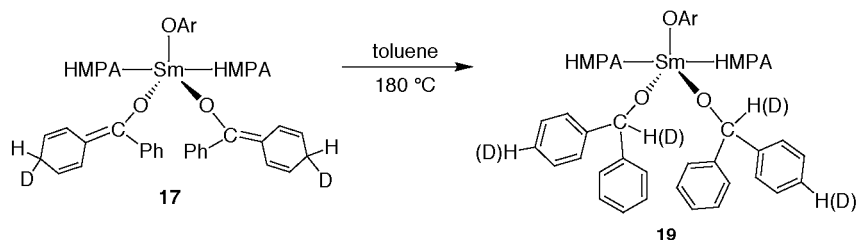**Scheme 15**
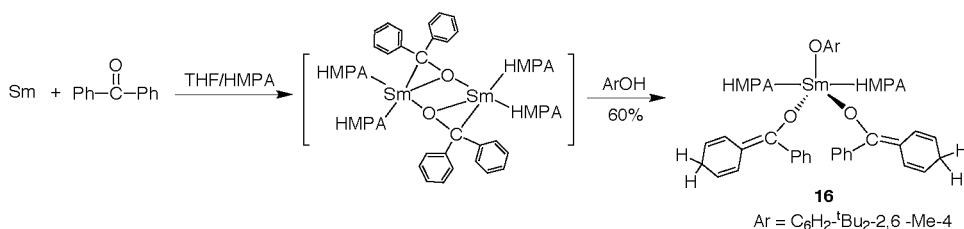
Scheme 16

Scheme 17

Scheme 18

deuterated enolate **17** (Scheme 17), suggesting that the formation of **15** and **16** is via the direct protonation of the para carbon atom of a phenyl group in the benzophenone dianion unit.

The formation of the enolate complexes **15** and **16** is apparently due to the delocalization of the negative charges in the phenyl groups of the benzophenone dianion species (see Scheme 13). The difference in reactivities observed between Sm(II) and Yb(II) benzophenone dianion species may result from differences in the two divalent metal ions. Since Sm(II) is more electron-donating [28] and bigger in size than Yb(II) [29], the negative charges in the Sm(II) benzophenone dianion species must be more delocalized into its phenyl rings, which are thus more easily protonated on the phenyl part and give a Sm(III) enolate species.

It is also interesting to note that the formation of the enolates **15** and **16** in the above reactions resembles well the Birch reduction of aromatic compounds bearing electron-withdrawing groups [30], in which metal enolate intermediates are believed to be formed via monoprotonation of dianionic species. However, such species have never been well characterized. Complexes **15** and **16** are

Scheme 19

rare examples of structurally characterized metal enolate compounds which model the enolate intermediates formed in the Birch reductions.

When the enolate complex **16** was heated in toluene or toluene-d_8 at 180 °C overnight, intramolecular hydrogen transfer reaction occurred to give the corresponding aryloxide/diphenylmethoxide complex $Sm(OC(H)Ph_2)_2(OAr)(HMPA)_2$ (**18**) (Scheme 18) [22, 24]. The similar reaction of the deuterated enolate **17** yielded **19** selectively (Scheme 19); scrambling of deuterium at the phenyl ring was not observed. These results suggest that the formation of **18** from **16** is a one-step 1,5-hydrogen shift process. It is also noteworthy that even at high temperatures (up to 180 °C) ligand redistribution in these heteroleptic lanthanide complexes was not observed.

3.3.2
Fluorenone Dianion Species

The protonation reaction of the Yb(II) fluorenone dianion species with ArOH is similar to the major reaction of the Yb(II) benzophenone dianion **14** with ArOH, occurring at both the C and O atoms of the carbonyl unit to afford **1d** and fluorenol (Scheme 20). However, the protonation reaction of the Sm(II) fluorenone dianion species with ArOH takes place only at the C atom and is accompanied by the oxidation of the Sm(II) ion to give the corresponding samarium(III) aryloxide/fluorenoxide complex **20** (Scheme 20), which again demonstrates the metal dependence of the reactivity of lanthanide ketone dianion species [22].

4
Ketone-Reduction Paths Based on Isolated Intermediates

As described above, with the combination of appropriate lanthanide reducing agents, solvents, and substrates, almost all types of the key intermediates involved in the reduction of ketones have been isolated and structurally characterized (Scheme 21), such as the one-electron reduction product (ketyl radical **21**), its reversible coupling product (pinacolate **24**), hydrogen abstraction product (alkoxide **23**) and further one-electron reduction product (ketone dianion **22**), and the selective protonation products of the ketone anion (alkoxide **23** and eno-
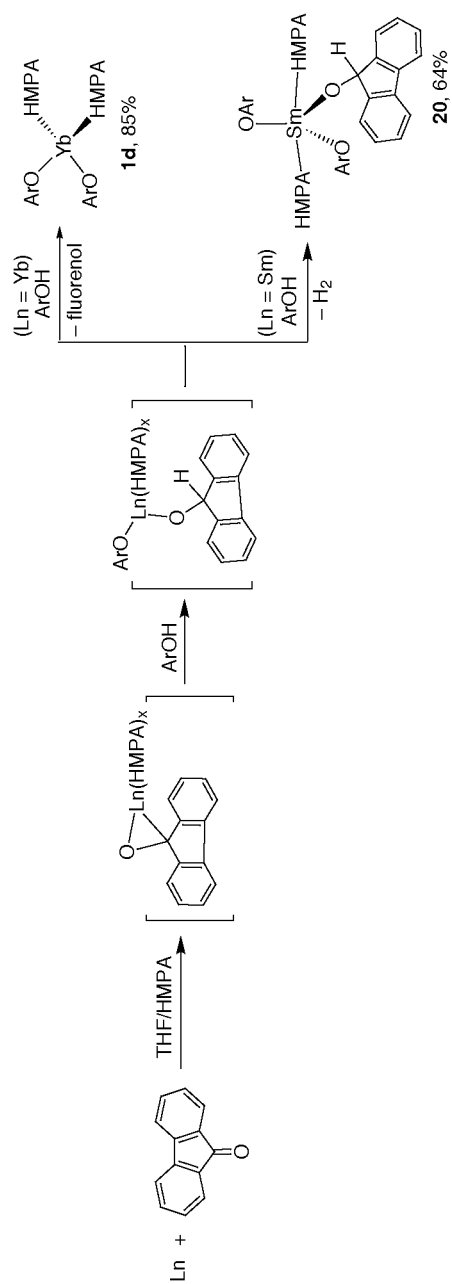
Scheme 20
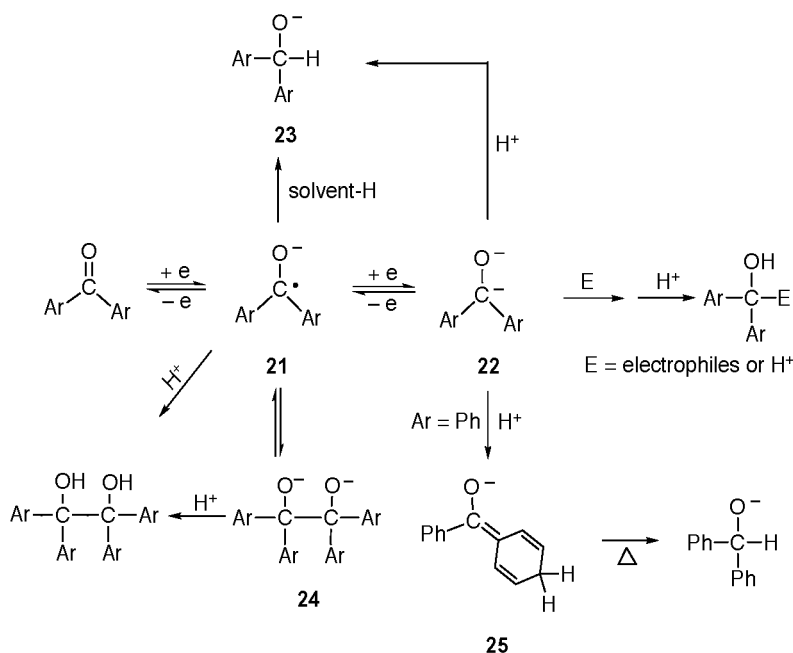
**Scheme 21.** Structurally characterized intermediates and their reactions

late **25**). Structural and reactivity studies of these isolated intermediates have given rise to an ever clearer picture of the reaction paths in the reaction of ketones with low-valent lanthanides (Scheme 21), and thus offered unprecedented insights into the mechanistic aspects of these and related reactions.

5
Dianionic Thioketone and Imine Species

Similar to diaryl ketones, aromatic thioketones and imines can also be reduced to the corresponding dianionic species. Fujiwara and coworkers have reported that the ytterbium diaryl thioketone dianion species, generated by reaction of Yb metal with the thioketones in THF/HMPA at low temperature, show good nucleophilicity towards organic substrates such as acetone and alkyl halides (Scheme 22) [31]. The thioketone dianion species seemed to be less stable than those of ketones. At room or higher temperatures, C-S bond cleavage reaction took place.

Reaction of *N*-(diphenylmethylidene)aniline with 1 equivalent of Yb metal in THF/HMPA gives the corresponding dianionic complex Yb(h^2-Ph$_2$CNPh)(HMPA)$_3$ (**26**) whose structure has been crystallographically determined (Scheme 23) [32]. The imine dianion complex **26** is more basic and less nucleophilic than ketone- and thioketone-dianion species. It reacts with CO$_2$ to give after hydrolysis the corresponding Yb(III) amino acid derivative [33], but with acetone to release

Scheme 22

Scheme 23

26, red-black
45%
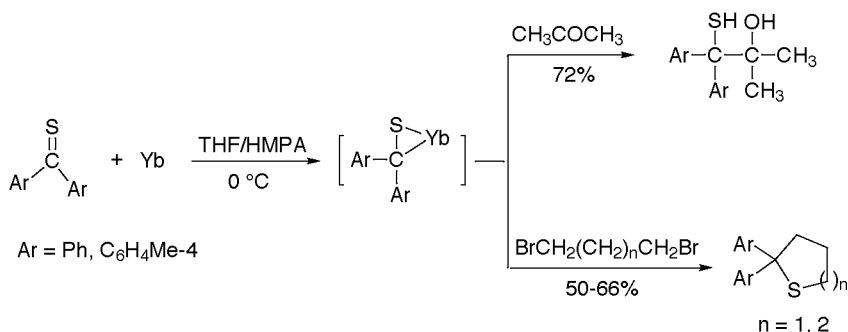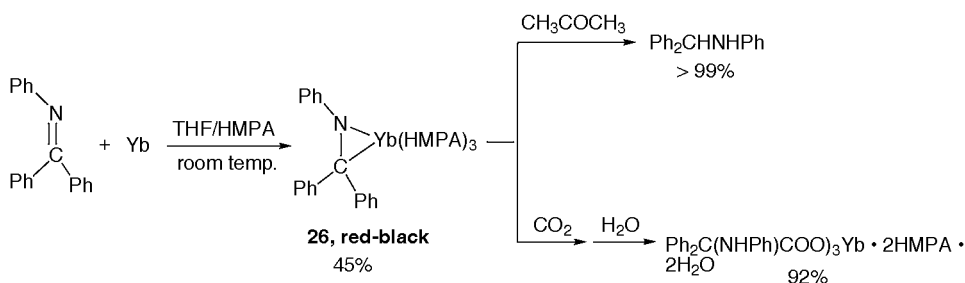
Ph$_2$CHNHPh almost quantitatively (Scheme 23) [32]. Isomerization of terminal alkynes to internal alkynes by 26 was also reported [34].

6
Conclusions and Perspectives

The results described in this article have clearly demonstrated that the highly reactive lanthanide ketyl and ketone dianion species can not only be isolated but also their reactivity be controlled through adjusting the environment around the central metals. For example, a ketyl species can be "deactivated" (stabilized) by binding to a bulky metal moiety and "reactivated" by reducing the bulkiness around the metal. Although the examples presented here are limited to those of aromatic ketones, these data should be conceptually useful for the understanding and design of reactions involving other organic carbonyl compounds. In view of the versatile uses of ketyls in organic synthesis and the high nucleophilicity of lanthanide ketone dianion species, if the "deactivation" and "reactivation" of alkyl ketone and/or aldehyde ketyl species can be achieved in a controllable way, and if alkyl ketone and/or aldehyde dianion species can also be generated, numerous classical C-C bond formation processes will be substan-

tially improved and our capability to access a variety of new target compounds will be dramatically enhanced. These topics remain to be challenged.

7
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Organo Rare Earth Metal Catalysis for the Living Polymerizations of Polar and Nonpolar Monomers

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This article deals with the rare earth metal initiated polymerization of polar and nonpolar monomers in a living fashion. For example, $[SmH(C_5Me_5)_2]_2$ or $LnMe(C_5Me_5)_2(THF)$ (Ln= Sm, Y and Lu) conducted the polymerization of methyl methacrylate(MMA) to give high molecular weight syndiotactic polymers (M_n>500,000, syndiotacticity>95%) quantitatively at low temperature (–95 °C). The initiation mechanism was discussed on the basis of X-ray analysis of the 1:2 adduct of $[SmH(C_5Me_5)_2]_2$ with MMA. Synthesis of high molecular weight isotactic poly(MMA) with very narrow molecular weight distribution was for the first time realized by the efficient catalytic function of $Yb[C(SiMe_3)_3]_2$. Living polymerizations of alkyl acrylates (methyl acrylate, ethyl acrylate, and butyl acrylate) were also possible by the excellent catalysis of $LnMe(C_5Me_5)_2(THF)$ (Ln=Sm, Y). By taking advantages of the living polymerization ability, we attempted ABA triblock copolymerization of MMA/butyl acrylate/MMA to obtain rubber-like elastic polymers. Organo rare earth metal complexes such as $LnOR(C_5R_5)_2$ or $LnR(C_5R_5)_2$ conducted the living polymerizations of various lactones such as β-propiolactone, δ-valerolactone and ε-caprolactone, and also conducted the block copolymerizations of MMA with various lactones. Lanthanum alkoxide(III) has good catalytic activity for the polymerization of alkyl isocyanates. Monodisperse polymerizations of lactide and various oxiranes were also achieved by the use of rare earth metal complexes. C_1 symmetric bulky organolanthanide(III) complexes such as $SiMe_2[2(3),4-(SiMe)_2C_5H_2]_2LnCH(SiMe_3)_2$ (Ln=La, Sm, and Y) show high catalytic activity towards linear polymerization of ethylene. Organolanthanide(II) complexes such as *racemic* $SiMe_2(2-SiMe_3-4-tBu-C_5H_2)_2Sm(THF)_2$ as well as C_1 symmetric $SiMe_2[2(3),4-(SiMe_3)_2C_5H_2]_2Sm(THF)_2$ were found to have high activity for the polymerization of ethylene to give M_n>10^6 with M_w/M_n =1.6. Utilizing the high polymerization activity of rare earth metal complexes towards both polar and nonpolar monomers, block copolymerizations of ethylene with polar monomers such as methyl methacrylate and lactones were for the first time realized. 1,4-cis-Conjugated diene polymerization of 1,3-butadiene and isoprene became available by the efficient catalytic activity of $NdCl(C_5H_5)_2/AlR_3$ or Nd(octanoate)$_3$/AlR$_3$. The Ln(naphthenate)$_3$/AliBu$_3$ system allows selective polymerization of acetylene in *cis*-fashion.

Keywords: Living polymerization, Living copolymerization, Rare earth metal complexes, Alkyl methacrylate, Alkyl acrylates, Lactones, Ethylene, 1-Olefins, Conjugated dienes, Acetylene

1
Introduction

Recent development of various living polymerizations of polar and nonpolar monomers allows the synthesis of high molecular weight polymers with very narrow molecular weight distribution. The indispensable conditions for the ideal living polymers are (1) number-average molecular weight M_n>100,000, (2) polydispersity index M_w/M_n<1.05, (3)stereoregularity >95%, and (4) high conversion in a short period of time >95%. Even the famous living polystyrene system [1] and the Group Transfer system [2] do not simultaneously satisfy requirements (1) and (2). Recently, to satisfy a long desire of many polymer chemists, all these four requirements were found to be met in the rare earth metal-initiated polymerization of methyl methacrylate (MMA), which gave M_n>500,000 with M_w/M_n=1.02–1.03 (syndiotacticity >95%) [3]. More recently, we have found isotactic polymerization of MMA by the efficient catalysis of non-metallocene type single component complex, $Yb[C(SiMe_3)_3]_2$, to give the poly(MMA) of M_n>200,000 with M_w/M_n=1.1 in high yield (isotacticity >97%).

Alkyl acrylates were for the first time polymerized in a living fashion with the aid of the unique catalytic action of rare earth metal complexes [4]. Since these monomers have an acidic α-H, termination and chain transfer reactions occur so frequently that their polymerizations generally do not proceed in a living manner. By taking advantages of the living polymerization ability of both MMA and alkyl acrylate, ABA or ABC type tri-block copolymerization was performed to obtain thermoplastic elastomers.

Living polymerization of lactones has been successfully performed by the catalysis of rare earth metal complexes producing M_w/M_n values of 1.07–1.08 [5]. Polymerizations of acrylonitrile and alkyl isocyanates have been successfully realized using $La[CH(SiMe_3)_2]_2(C_5Me_5)$ as initiator, and those of various oxiranes have been made using $Ln(acac)_3/AlR_3/H_2O$ system [6].

Organo rare earth metal initiators also show good activity towards non-polar monomers such as ethylene, 1-olefins, styrene, conjugated dienes, and acetylene

derivatives. In fact, poly(ethylene) of M_n>1,000,000 with M_w/M_n=1.6 was made available by the use of a C_1 symmetric divalent complex, $Me_2Si[2(3),4-(SiMe_3)_2C_5H_2]_2Sm(THF)_2$. However, the magnitude of M_n for poly(olefin)s such as poly(1-pentene), polystyrene, and poly(1,5-hexadiene) were not made high enough even with the help of the characteristic catalytic action of rare earth metal complexes. The maximum M_n of 60,000 obtained for poly(1-hexene) was still far below the desired minimum of 400,000. Conjugated dienes and acetylene derivatives were polymerized by the use of rather complex rare earth metal catalysts, but the resulting M_w/M_n remained fairly large. The use of a mononuclear single-site catalyst is required for the polymerization of these derivatives.

2
Highly Stereospecific Living Polymerization of Alkyl Methacrylates

Although various living polymerization systems have been proposed, any of anionic [7], cationic [8], Group Transfer [2], and metal carbene initiated polymerizations [9] achieved no success in synthesizing living polymers of M_n>500,000 with M_w/M_n<1.05. On the other hand, high molecular weight poly(MMA) having an unusually low polydispersity has been synthesized by utilizing the unique initiating function of organolanthanide(III) complexes (Fig. 1) [3]. The relevant complexes include lanthanide hydrides, bulky alkyl lanthanide, bis-Me-bridged trimethylaluminum complexes of alkyllanthanides, and simple alkyl complexes (Fig. 2). The results of the polymerization of MMA with $[SmH(C_5Me_5)_2]_2$ initiator at different temperatures are summarized in Table 1. The most striking is very narrow molecular weight distributions, i.e. M_w/M_n=1.02–1.04 for M_n>60·10^3. Remarkably, $[SmH(C_5Me_5)_2]_2$ complexes give high conversion (polymer yield) in a relatively short period, and allow the polymerization to proceed over a wide range of reaction temperatures from –78 to 40 °C. Furthermore, syndiotacticity exceeding 95% is obtained when the polymerization temperature is lowered to –95 °C.

The typical initiator systems reported so far for the synthesis of highly syndiotactic poly(MMA) are bulky alkyllithium $CH_3(CH_2)_4CPh_2Li$ [10], Grignard reagent in THF [11], and some AlR_3 complexes [12]. Although the
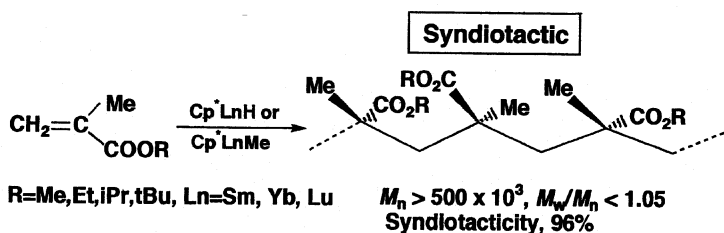

Fig. 1. Organolanthanide initiated syndiotactic polymerization of MMA

Fig. 2. X-ray analysis of Sm(C$_5$Me$_5$)$_2$(MMA)$_2$H

Table 1. Characterization of monodisperse poly(MMA) synthesized by [SmH(C$_5$Me$_5$)$_2$]$_2$ initiator

Polymerization temperature(°C)	MMA/initiator charged(mol/mol)	$M_n \cdot 10^3$	M_w/M_n	rr %	Conversion/% (react. time)
40	500	55	1.03	77.3	99 (1 h)
0	500	58	1.02	82.4	99 (1 h)
0	1500	215	1.03	82.9	93 (2 h)
0	3000	563	1.04	82.3	98 (3 h)
−78	500	82	1.04	93.1	97 (18 h)
−95	1000	187	1.05	95.3	82 (60 h)

M_n and M_w/M_n were determined by GPC using standard poly(MMA) with M_w measured by light scattering method. Solvent, toluene; solvent /[M]$_0$=5 (vol/vol).

CH$_3$(CH$_2$)$_4$CPh$_2$Li initiator in THF conducted the polymerization of MMA at −78 °C, the M_n reached only 10,000 with M_w/M_n=1.18, while it gave isotactic polymers in toluene. iBuMgBr and CH$_2$=CHC$_6$H$_4$CH$_2$MgBr in THF at lower temperature also gave high syndiotactic poly(MMA) but M_n remained as low as 14,000–18,000 and the yields were quite low. When iBuMgBr or tBuMgBr was used in toluene instead of THF, the resulting poly(MMA) had a high iso-tacticity of 96.7% with M_n=19,900 and M_w/M_n=1.08 [13]. AlEt$_3$.PR$_3$ complexes gave high syndiotacticity, but not a high molecular weight.

Ketene silyl acetal/nucleophilic agent systems initiate the polymerization of alkyl methacrylates. These well-known Group Transfer systems yielded living polymers with atactic sequences at relatively high temperature [2]. Me$_2$C= C(OMe)OSiR$_3$ and R$_2$POSiMe$_3$ can be used as initiators, and tris(dimethylami-no)sulfonium bifluoride and Et$_4$CN are frequently used as catalysts. For exam-ple, the M_w/M_n of the resulting poly(MMA) was 1.06 for M_n=3800, and 1.15 for

M_n=6300. Thus, we conclude that organolanthanide-initiated polymerization is superior to other catalysts in obtaining monodisperse high molecular weight poly(MMA).

These findings motivated us to isolate the 1:1 or 1:2 adduct of $[SmH(C_5Me_5)_2]_2$ with MMA in order to elucidate the initiation mechanism. After expending much effort, we have obtained the desired 1:2 adduct as an airsensitive orange crystal (mp 132 °C). The X-ray analysis of the adduct indicates that one of the MMA unit is linked to the metal in an enolate form while at the other end the penultimate MMA unit is coordinated to the metal through its C=O group. Thus an 8-membered cyclic intermediate was formed (Fig. 3).

Although similar cyclic intermediates have been proposed by Bawn and Ledwith [14] and Cram and Copecky [15] for the isotactic polymerization of MMA, no isolation of such active species has succeeded. On the basis of the X-ray structural data as well as the observed mode of polymerization, we can propose a coodination anionic mechanism involving an 8-membered transition state for the present organo rare-earth metal initiated polymerization of MMA. In the initiation step, the hydride attacks the CH_2 group of MMA, and a transient $SmOC(OCH_3)=C(CH_3)_2$ species should be formed. Then the incoming MMA molecule is supposed to participate in the 1,4-addition to produce an 8-membered cyclic intermediate. Further addition of MMA to the 1:2 addition compound results in liberation of the coordinated ester group and the 8-membered cyclic intermediate is again generated. The intermolecular repulsion between C(7) and C(9) (or the polymer chain) should be the essential factor in determining the syndiotacticity. The addition of 100 molar amounts of MMA to the 1:2 adduct yielded poly(MMA) of M_n=ca. $110 \cdot 10^3$ and M_w/M_n=1.03, proving that the 1:2 adduct is a real active species. Thus, initiation process occurs much faster than the propagation process.
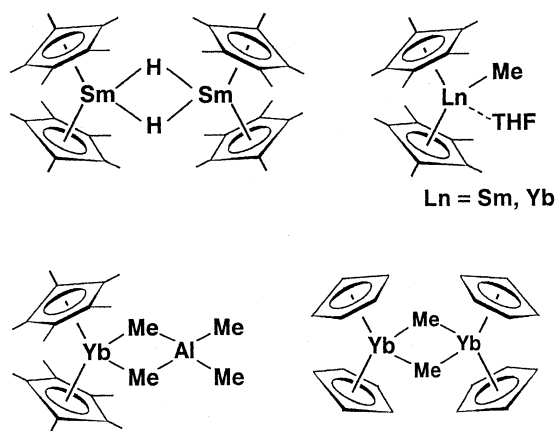

Fig. 3. Typical initiator used for the living polymerization of MMA

On the other hand, monodisperse isotactic poly(MMA) has been obtained with *t*BuMgBr in toluene at −40 °C (M_n=10.1· 10^3, M_w/M_n=1.08, isotacticity =96.7%) [16] or *sec*BuMgBr in toluene at −78 °C (M_n=4.9· 10^3, M_w/M_n=1.29, isotacticity =95.5%) [16]. Synthesis of isotactic poly(MMA) with much higher molecular weight is required. Recently, high molecular weight isotactic poly(MMA) (mm= 97%, M_n=500,000, M_w/M_n=1.12) was first obtained quantitatively by the use of a non-metallocene type rare earth complex [$(Me_3Si)_3C]_2$Yb (Fig. 4) [17]. We propose here the initiation mechanism as noted below through noncyclic intermediate for this isotactic polymerization of MMA (Fig. 5). The polymerization should proceed by the enantiomorphic site control in toluene. In contrast, syndiotactic polymer was obtained when THF was used as solvent (rr=87%, M_n= 3.2· 10^4, M_w/M_n=1.76) presumably due to chain end control through cyclic intermediate. By utilizing the resulting isotactic polymer, we have prepared a stereo-complex between isotactic and syndiotactic polymers by mixing these two polymers in acetone in a 1:2 ratio (Fig. 6). The resulting stereo-complex shows the intermediate physical property between the homo-isotactic and homo-syndotactic polymers (Table 2). Isotactic polymerization of MMA has also been achieved (mm=94%, M_n=134· 10^3, M_w/M_n=6.7) by using $Me_2Si(C_5Me_4)[C_5H_3$-(1S),(2S),(5R)-neomenthyl]LaR (R=CH(SiMe_3)_2 or N(SiMe_3)_2) [18], while $Me_2Si(C_5Me_4)[C_5H_3$-(1S),(2S),(5R)-menthyl]LnR (Ln=Lu, Sm; R=CH(SiMe_3)_2 or N(SiMe_3)_2) complex produces syndiotactic poly(MMA) (rr=69%, M_n=177· 26010^3, M_w/M_n=15.7). Polydispersity is rather wide in these cases.
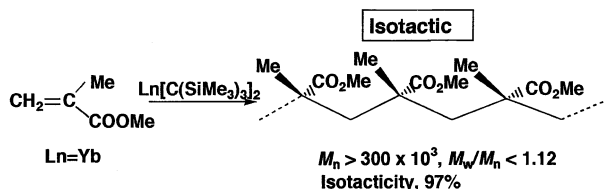

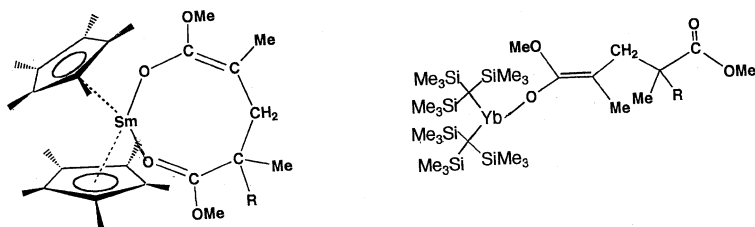**Fig. 4.** Isotactic polymerization of MMA catalyzed by rare earth metal complex

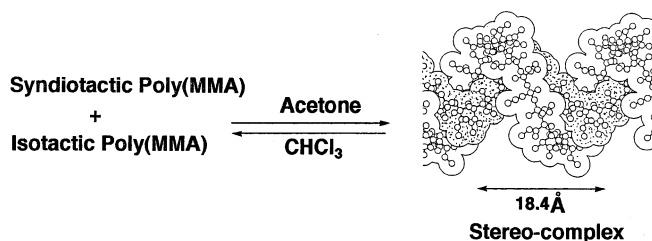**Fig. 5.** Proposed intermediates for syndiotactic and isotactic polymerization of MMA

Fig. 6. Preparation of stereo-complex between isotactic and syndiotactic poly(MMA)

Table 2. Mechanical properties of isotactic, syndiotactic poly(MMA) and the stereo-complex

	Tensile modulus kgf/mm^2	Tensile strength kgf/mm^2	Elongation %
isotactic poly(MMA)	2.0	30.2	435
syndiotactic poly(MMA)	10.0	116.1	13
stereo-complex	4.6–5.8	86–121	20–30

Boffa and Novak found a divalent rare earth metal complex, $Sm(C_5Me_5)_2$, to be a good catalyst for polymerization of MMA [19]. The initiation started with the coupling of two coordinated MMA molecules to form Sm(III) species. The bis-allyl initiator, $Sm(\eta^3\text{-}CH_2\text{-}CH\text{-}CH)_2(C_5Me_5)_2$, was also effective for living polymerization of MMA. In this case, MMA must add to both ends of the hexadiene group. In the polymerization of MMA initiated with methylaluminum tetraphenylporphyrine, crowded Lewis acid such as MeAl(ortho-substituted phenolate)$_2$ serves as a very effective accelerator without damaging the living character of polymerization [20]. Thus, the polymer produced has narrow polydispersity (M_w/M_n=1.09) and sufficiently high molecular weight, M_n=25,500, but the stereoregularity is very poor. The use of a simple organoaluminum such as trimethylaluminum causes the occurrence of preferred termination.

The organolanthanide initiators also allowed stereospecific polymerization of ethyl, isopropyl, and *tert*-butyl methacrylates. The rate of polymerization and syndiotacticity decreased with increasing bulkiness of the alkyl group in the order Me>Et>iPr>>tBu. Butyl methacrylate was also polymerized using Nd(octanoate)$_3$/AliBu$_3$ (Al/Nd=7–10), but the molecular weight distribution and stereoregularity were not reported [21].

In general, Ziegler-Natta catalysts such as $TiCl_4/MgCl_2/AlR_3$ and Kaminsky catalysts such as $Cp_2ZrCl_2/(AlMe_2\text{-}O\text{-})_n$ do not catalyze the polymerization of polar monomers. However, a mixture of cationic species $Cp_2ZrMe(THF)^+$ and Cp_2ZrMe_2 has been found to do so for MMA [17], allowing syndiotactic poly(MMA) (rr=80%, M_n=120,000, M_w/M_n=1.2–1.3) [22]. Recently, Soga et al. [23] reported the syndio rich polymerization of MMA catalyzed by $Cp_2ZrMe_2/Ph_3CB(C_6F_5)_4/ZnEt_2$ and also the isotactic po-

lymerization of MMA catalyzed by rac-Et(ind)$_2$ZrMe$_2$/Ph$_3$CB(C$_6$F$_5$)$_4$/ZnEt$_2$ (mm=96.5%, M_n=39.3 · 10^4, M_w/M_n=1.43). The observed characteristic nature of rare earth metal initiator may originate from large ionic radii (1.0–1.17 Å) and low electronegativity (1.0–1.2). Their ionic radii are much larger than those of main group metals (Li 0.73; Mg 0.71; Al 0.68 Å) and the electronegativities resemble those of Li (1.0) and Mg (1.2).

3
Living Polymerization of Alkyl Acrylates

Living polymerization of alkyl acrylates is usually very difficult because the chain transfer or temination occurs preferentially, owing to a high sensitivity of the acidic α-proton to the nucleophilic attack. Exceptions are the living polymerization of a bulky acrylic ester catalyzed by alkyllithium/inorganic salt (LiCl) systems as well as the Group Transfer polymerizations of ethyl acrylate using ZnI$_2$ as the catalyst. Porphyrinatoaluminum initiator systems also induced the living polymerization of $tert$-butyl acrylate [24], but the upper limit of molecular weight attained was ca. 20,000. We have found the efficient initiating properties of SmMe(C$_5$Me$_5$)$_2$(THF) and YMe(C$_5$Me$_5$)$_2$(THF) for living polymerization of acrylic esters (Table 3), i.e. methyl acrylate (MeA), ethyl acrylate (EtA), butyl acrylate (Bu), and $tert$-butyl acrylate (tBuA), although the reactions were non-stereospecific (Fig. 7) [25]. The initiator efficiency exceeded 90% except for tBuA. We therefore concluded that the reactions occur in living fashion. In fact, the M_n of poly(BuA) initiated by SmMe(C$_5$Me$_5$)$_2$(THF) increased linearly in pro-

Table 3. Polymerization of alkyl acrylates initiated by organolanthanide complexes

Initiator	Monomer	$M_n/10^3$	M_w/M_n	Tacticity/%			Conversion	
				rr	mr	mm	%	Efficiency %
[SmMe(C$_5$Me$_5$)$_2$(THF)]	MeA	48	1.04	30	50	20	99	89
	EtA	55	1.04	51		49	94	86
	nBuA	70	1.05	28	53	19	99	91
	tBuA	15	1.03	27	47	26	99	79

Polymerization conditions: 0 °C in toluene, initiator concentration 0.2 mol%.
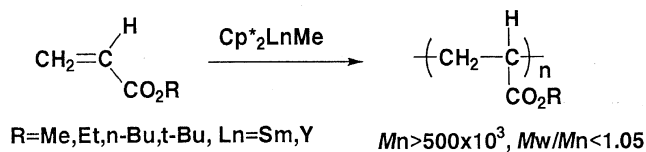

Fig. 7. Living polymerization of alkyl acrylates

portion to the conversion, while M_w/M_n remained unchanged, irrespective of the initiator concentration. In order to establish the characteristic nature of these initiation systems, the initiator concentration was decreased from 0.1 to 0.002 mol% of monomer and high molecular weight poly(EtA) of Mn=800,000 with narrow molecular weight distribution (Mw/Mn=1.05) was obtained.

ABA type triblock copolymerization of MMA/BuA/MMA should give rubber-like elastic polymers. The resulting copolymers should have two vitreous outer blocks, where the poly(MMA) moiety (hard segment) associates with the nodules, and the central soft poly(BuA) elastomeric block provides rubber elasticity. The first step polymerization of MMA gave M_n of 15,000 with M_w/M_n=1.04 and then a mixture of MMA and BuA was added to this growing end to result in the formation of desired ABA triblock copolymer (BuA polymerized more rapidly than MMA) (Fig. 8). Table 4 shows the typical mechanical properties of the ABA

Table 4. Mechanical properties of triblock copolymers

Copolymer	Tensile modulus (MPa)	Tensile strength (MPa)	Elongation (%)	Izod impact strength (J/m)	Compression set/% (70 °C, 22 h)
Poly(MMA)	610	80	21	18	100
poly(MMA/BuA/MMA) (20:47:33)	75	27	83	383 (N.B)	101
poly(MMA/BuA/MMA) (25:51:24)	46	22	8	390 (N.B)	103
poly(MMA/BuA/MMA) (8:72:20)	0.8	0.7	163	400 (N.B)	58
poly(MMA/BuA/MMA) (6:91:3)	0.2	0.1	246	410 (N.B)	97
poly(MMA/EtA/EtMA) (26:48:26)	119	22	276	34	62

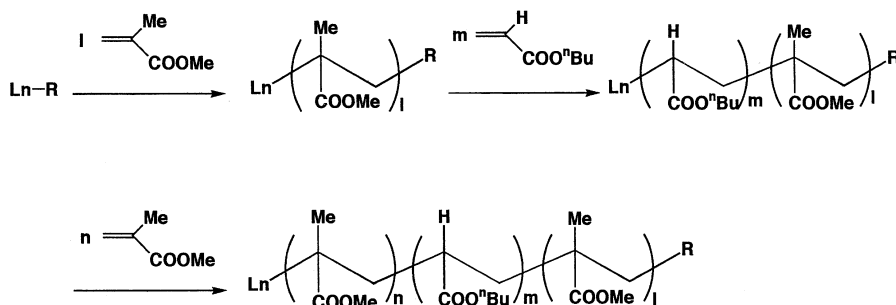N.B.; not break. EtA; ethylacrylate. EtMA; ethyl methacrylate

Fig. 8. ABA type block copolymerization of MMA/BuA/MMA

type copolymers thus obtained. Homo-poly(MMA) has large tensile modulus and large tensile strength, but is poor in elongation and shows very large compression set. In contrast, the triblock copolymer (8:72:20) shows 58% compression set and large elongation (163%), indicating that this polymer is a thermoplastic elastomer. The triblock copolymer of MMA/EtA/EtMA in the ratio of 26:48:26 also showed large elongation and small compression set. Thus, elastic copolymers of methacrylate with acrylate were for the first time obtained by using living polymerization ability of rare earth metal complexes.

4
Block Copolymerization of Hydrophobic and Hydrophilic Acrylates

Trimethylsilyl metacrylate (TMSMA) was found to proceed the living polymerization using $SmMe(C_5Me_5)_2$(THF) as initiator to give high molecular weight syndiotactic polymer (M_n=56,000, rr=92%) with very low polydispersity (M_w/M_n=1.09). By utilizing this nature, we have performed the block copolymerization of TMSMA with MMA or butyl acrylate to obtain the adhesive materials upon hydrolysis of the resulting polymer [26]. The result is shown in Table 5. Thus, block copolymerization of TMSMA with MMA (or BuA) gave thermally stable adhesive materials for the first time (high thermal stability originates from high syndiotacticity) (Fig. 9).
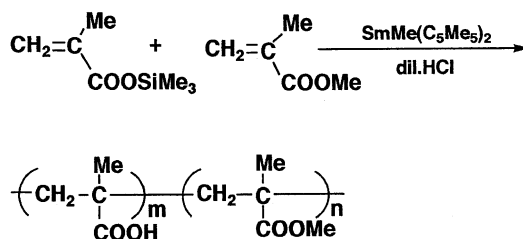

Fig. 9. Block copolymerization of MMA with TMSMA

Table 5. Block copolymerization of TMSMA with MMA or BuA

Feed ratio		M_n (calcd)	poly(TMSMA)		poly(TMSMA/MMA or BuA)		Yield/%
TMSMA	MMA		M_n	Mw/Mn	M_n	Mw/M_n	
67	124	23,000	8,900	1.13	28,100	1.17	99
TMSMA	BuA						
30	42	10,100	52,000	1.11	10,500	1.16	98
67	93	22,500	81,000	1.10	22,600	1.26	99
30	304	43,700	51,000	1.11	77,300	1.15	99

Solvent, toluene; Polymerization of TMSMA 2 min, Polymerization temp. 0 °C.

5
Polymerization of Alkyl Isocyanates

Polyisocyanates have attracted much attention owing to their liquid crystalline properties, stiff-chain solution characteristics, and induced optical activities associated with the helical chain conformation. Pattern and Novak discovered that such titanium complexes as $TiCl_3(OCH_2CF_3)$ and $TiCl_2(C_5H_5)(OCH_2CF_3)$ initiate the living polymerization of isocyanates at ambient temperature, giving polymers with narrow molecular weight distribution [27]. When hexyl isocyanate was added to $TiCl_3(OCH_2CF_3)$ the polymerization took place, to give M_n (M_w/M_n= 1.1–1.3) increasing linearly with the initial monomer-to-initiator mole ratio or the monomer conversion over a wide range. Recently, Fukuwatari et al. found lanthanum isopropoxide to serve as a novel anionic initiator for the polymerization of hexyl isocyanate at low temperature (–78 °C), which led to very high molecular weight ($M_n > 10^6$) and rather narrow molecular weight distribution (M_w/M_n=2.08–3.16) [28]. Other lanthanide alkoxides such as $Sm(OiPr)_3$, $Yb(OiPr)_3$, and $Y(OiPr)_3$ also induced the polymerization of hexyl isocyanate. Furthermore, it was shown that butyl, isobutyl, octyl and *m*-tolyl isocyanates were polymerized using lanthanum isopropoxide as initiator. However, *tert*-butyl and cyclohexyl isocyanates failed to polymerize with these initiators under the same reaction conditions. When the reaction temperature was raised to ambient temperature, only cyclic trimers were produced at high yields. More recently we have found that $La(C_5Me_5)_2[CH(SiMe_3)]_2$ also initiates the polymerization of hexyl isocyanate in 90–96% yields in THF at –20 to –40 °C (M_n=59· 10^4, M_w/M_n=1.57–1.90) [29] (Fig. 10).

6
Living Polymerization of Lactones

$AlEt_3$-H_2O or $AlEt_3$-catalyzed polymerizations of 3-methyl-β-propiolactone and ε-caprolactone have been reported [30, 31] but this type of polymerization generally gives a broad molecular weight distribution. We have explored the polymerization of various lactones including β–propiolactone (PL), 3-methyl-β-propiolactone (MePL), δ-valerolactone (VL) and ε-caprolactone initiated by single organolanthanides, and found that VL and CL led to the living polymerization (Fig. 11) , yielding polymers with M_w/M_n=1.05–1.10 at quantitative yields (Table 6). For ε-caprolactone, M_n obtained with the $SmMe(C_5Me_5)_2(THF)$ or

Fig. 10. Living polymerization of alkyl isocyanate
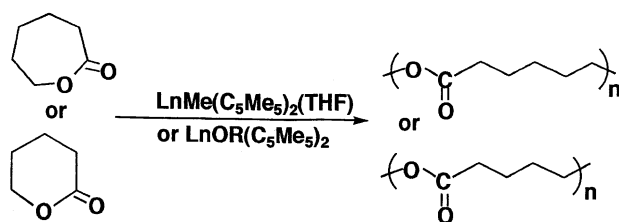
Fig. 11. Living polymerization of lactones

Table 6. Living polymerization of lactones with organolanthanide complexes

Initiator	Monomer	$M_n/10^3$	M_w/M_n	Conversion/%
SmMe(C$_5$Me$_5$)$_2$(THF)	VL	75.2	1.07	80.1 (7 h)
	CL	109.4	1.09	92.0 (7 h)
[SmH(C$_5$Me$_5$)$_2$]$_2$	VL	65.7	1.08	90.5 (7 h)
	CL	71.1	1.19	88.7 (5 h)
[YOMe(C$_5$H$_5$)$_2$]$_2$	CL	162.2	1.10	87.5 (5 h)
	PL	60.5	3	94.5 (5 h)

PL β-propiolactone, VL δ-varelolactone, CL ε-caprolactone. Polymerization, 0 °C in toluene.

[SmH(C$_5$Me$_5$)$_2$]$_2$ system increased with increasing conversion, but M_w/M_n remained constant, irrespective of the conversion. For β-propiolactone, the use of YOR(C$_5$Me$_5$)$_2$ was more favorable. On the other hand, divalent organolanthanide complexes can initiate the polymerization of lactones, but the resulting polymers had rather broad molecular weight distributions.

At the early stage of the polymerization of lactone with Ln(OR)(C$_5$Me$_5$)$_2$, one mole of ε-caprolactone coordinates to the metal, as is the case for the reaction of YCl$_3$ with ε-caprolactone, giving the six-coordinate mer complex, YCl$_3$·(ε-caprolactone)$_3$, in which each caprolactone molecule is coordinated as a monodentate ligand through its carbonyl oxygen [32]. The polymerization starts with the coordination of ε-caprolactone to form the 1:1 complex, Ln(OR)(C$_5$Me$_5$)$_2$ (ε-caprolactone) (Fig. 12), and in its propagation step the alkoxide attacks the C=O group to produce Ln[O(CH$_2$)$_5$C(O)OR](C$_5$Me$_5$)$_2$ (ε-caprolactone) [5]. In the SmMe(C$_5$Me$_5$)$_2$ initiator system, the reaction is initiated by the attack of ε-caprolactone or δ-valerolactone to result in the formation of an acetal without ring opening. This process has been confirmed by ^{13}C NMR studies on the stoichiometric reaction products.

Anionic block copolymerizations of MMA with lactones proceeded smoothly to give copolymers with M_w/M_n=1.11–1.23 when the monomers were added in this order (Fig. 13).

However, when the order of addition was reversed, no copolymerization took place, i.e. no addition of MMA to the polylactone active end occurred [5].
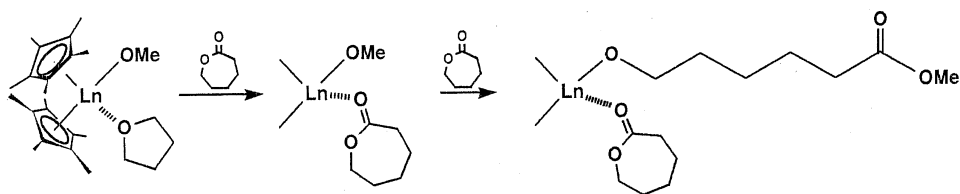
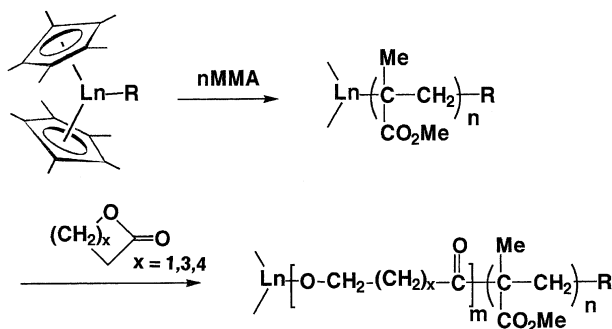**Fig. 12.** Initiation mechanism for polymerization of lactones

Fig. 13. Copolymerization of MMA with lactones

7
Stereospecific Polymerization of Oxiranes

Organolanthanide(III) complexes such as $LnMe(C_5Me_5)_2$ or $LnH(C_5Me_5)_2$ do not initiate the polymerization of oxirans, but more complex systems like $Ln(acac)_3/AlR_3/H_2O$ and $Ln(2\text{-EP})_3/AlR_3/H_2O$ (2-EP; di-2-ethylhexylphosphate) polymerize with good initiation activity [33]. High molecular weight poly(ethylene oxide) is one of the common water-soluble polymers useful as adhesives, surfactants, plasticizers, and dispersants as well as for sizing material. Poly(ethylene oxide) of $M_n=2.85 \cdot 10^6$ was obtained with the $Y(2\text{-}EP)_3/AliBu_3/H_2O$ system at the ratio of $Y/Al/H_2O=1/6/3$. The initiator activity varies with the molar ratio of the components. Polymerization of propylene oxide was reported to proceed with the $Ln(acac)_3/AlEt_3/H_2O$ system, and light rare earth elements (Y, La, Pr, Nd, Sm) produced very high molecular weight poly(propylene oxide) at $Al/Ln=6$ in a short period of time (2 h) in toluene [34]. The $Nd(acac\text{-}F_3)_3/AlR_3/H_2O$ (Ln=Y, Nd) systems [35] gave isotactic poly(propylene oxide), while the $Cp_2LnCl/AlR_3/H_2O$, $Sm(OiPr)_3/AlR_3/H_2O$ or Y(2-ethylhexanoate)$_3$/AlR$_3$/H$_2$O system produced relatively low molecular weight isotactic species of this polymer (Fig. 14).
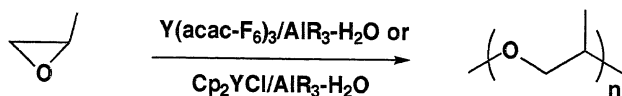
Fig. 14. Rare earth metal initiated polymerization of oxirans
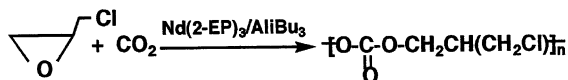

Fig. 15. Copolymerization of epichlorohydrine with CO_2

Random copolymerization of propylene oxide with ethylene oxide proceeded smoothly with the $Nd(2-EP)_3/AlEt_3/H_2O$ system at 80 °C [36]. From the copolymerization composition curve, the monomer reactivity ratios were evaluated to be $r_1(EO)=1.60$ and $r_2(PO)=0.45$. The conversion increased with an increase in the Al/Nd ratio and saturated at a molar ratio of 16. Since the $Nd(2-EP)_3/AlEt_3/H_2O$ system generates a growing poly(propylene oxide) chain having a very long life, block copolymerization with ethylene oxide can be achieved successfully. The $Ln(acac)_3/AliBu_3/H_2O$ (1:8:4) systems, especially in the case of Nd derivative, also initiated the polymerization of epichlorohydrin (EPH) to yield a polymer of $M_v=16.5\cdot 10^5$ with 21% crystallinity. Toluene is used preferably but aliphatic hydrocarbons is not suitable because poly(epichlorohydrin) precipitates from the solvent during the polymerization. The relative monomer reactivities evaluated for the propylene oxide (PO)-allyl glycidylether(AGE) system were $r_1(PO)=2.0$ and $r_2(AGE)=0.5$, and those for the epichlorohydrin-AGE system were $r_1(EPH)=0.5$ and $r_2(AGE)=0.4$ [37]. This combination of monomer reactivity ratios indicates that the polymerization with $Ln(acac)_3/AliBu_3/H_2O$ follows a coordination anionic mechanism, but that with the $AliBu_3/H_2O$ system does cationic polymerization mechanism.

Although the copolymerization of propylene oxide with CO_2 takes place effectively with the organozinc-additives or the (tetraphenyl)porphyrin-AlCl system [38], the copolymerization of epichlorohydrine with CO_2 hardly occurs with these catalysts. Shen et al. [39] showed that a rare earth metal catalyst such as the $Nd(2-EP)_3/AliBu_3$ (Al/Nd=8) system was very effective for the copolymerization of epichlorohydrine with CO_2 (30–40 atm) at 60 °C (Fig. 15). The content of CO_2 in the copolymer reached 23–24 mol% when 1,4-dioxane was used as solvent.

The $ZnEt_2/H_2O$ [40], $AlEt_3/H_2O$ [41], and Cd salt [42] systems are well-known initiators for the polymerization of propylene sulfide. Shen et al. [43] examined this polymerization with the $Ln(2-EP)_3/AliBu_3/H_2O$ system and found that high molecular weight polymers were produced at a low concentration of Nd ($6.04\cdot 10^{-3}$ mol/l) at the ratio of $Nd/Al/H_2O=1/8/4$. The polymerization activity decreased in the order Yb=La>Pr>Nd=Eu>Lu>Gd>Dy>Ho>Er. The ^{13}C-NMR spectrum indicated that β-cleavage occurs preferentially over the α-cleavage

and the ratio of these ring openings changes little with the initiator system and the polymerization temperature. The polymers obtained were amorphous according to DSC and XRD analyses.

8
Polymerization of Lactide

Shen et al. [44] succeeded ring opening polymerization of D,L-lactide (racemic species) using Nd(naphthenate)$_3$/AliBu$_3$/H$_2$O (1:5:2.5), Nd(P$_{204}$)$_3$/AliBu$_3$/H$_2$O (P$_{204}$=[CH$_3$(CH$_2$)$_3$CH(CH$_2$CH$_3$)CH$_2$O]$_2$P(O)OH], and Nd(P$_{507}$)$_3$/AliBu$_3$ /H$_2$O (P$_{507}$=(iC$_8$H$_{17}$O)$_2$P(O)OH) systems, obtaining the polymers whose molecular weights were M_n=3.1–3.6·10^4 and the conversions larger than 94%. When the Ln(naphthenate)$_3$/AliBu$_3$/H$_2$O system was used, nearly the same results were obtained irrespective of the metals used (La, Pr, Sm, Gd, Ho, Tm). Divalent (2,6-tBu$_2$-4-Me-phenyl)$_2$Sm(THF)$_4$ was also found to be active for the polymerization of D,L-lactide at 80 °C in toluene, giving M_n of 1.5–3.5·10^4 [45]. A more recent finding is that the Ln(O-2,6-tBu$_2$-C$_6$H$_3$)$_3$/iPrOH (1:1–1:3) system initiates a smooth homo-polymerization of L-lactide, CL (caprolactone) and VL (valerolactone) to give relatively high molecular weights (M_n>24·10^3) with low polydispersity indices (M_w/M_n=1.2–1.3) (Fig. 16) [46]. Ring-opening polymerization of D,L-lactide was also carried out by using Ln(OiPr$_3$)$_3$ as the catalyst at 90 °C in toluene. The catalytic activity increased in the order La>Nd>Dy>Y and the molecular weight reaches 4.27·10^4(conversion 80%) [47]. However, the molecular weight distribution is not clear at present. The block copolymerization of CL with L-lactide proceeded effectively and gave a polymer of very narrow molecular weight distribution (M_w/M_n=1.16). On the other hand the addition of CL to the living poly(L-lactide) end led to no success.

9
Stereospecific Polymerization of Olefins

Bulky organolanthanide(III) complexes such as LnH(C$_5$Me$_5$)$_2$ (Ln=La, Nd) were found to catalyze with high efficiency the polymerization of ethylene. These hydrides are, however, thermally unstable and cannot be isolated as crystals. Therefore, thermally more stable bulky organolanthanides were synthesized by
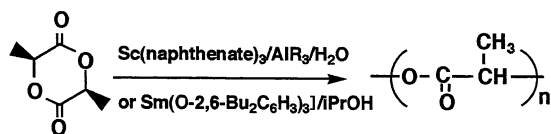

Fig. 16. Polymerization of D,L-lactide

introducing four trimethylsilyl groups into the Me$_2$Si bridged Cp ligand, as shown in Fig. 17. The reaction of the dilithium salt of this ligand with anhydrous SmCl$_3$ produced a mixture of two stereo-isomeric complexes. The respective isomers were isolated by utilizing their different solubilities in hexane, and their structures were determined by X-ray crystallography. One of them has a C_2 symmetric (racemic) structure in which two trimethylsilyl groups are located at the 2,4-positions of the Cp rings, while the other has a C_1 symmetric structure in which two trimethylsilyl groups are located at 2,4- and 2,3-positions of each Cp ring. Both were converted to alkyl derivatives when they were allowed to react with bis(trimethylsilyl)methyllithium [48]. The Cp'-Sm-Cp' angle of the *racemic* precursor is 107°, which is about 15° smaller than that of non-bridged SmMe(C$_5$Me$_5$)$_2$(THF).

Meso type ligands were synthesized by forcing two trimethylsilyl groups to be located at the 4-position of the ligand with introduction of two bridges. Actually, the complexation of this ligand with YCl$_3$ yielded a *meso* type complex, and the structure of the complex was determined by X-ray analysis. The *meso* type alkyl complex was synthesized in a similar manner [49]. Table 7 summarizes the results of ethylene polymerization with these organolanthanide(III) complexes. Interestingly, only C_1 type complexes can initiate the polymerization, implying that the catalytic activity varies with the structure of the complex. The X-ray structure of the C_1 symmetric complex is given in Fig. 18, where the Cp'-Sm-Cp' angle is seen to be 108°, a very small dihedral angle. The polymerization of ethylene with SmH(C$_5$Me$_5$)$_2$ in the presence of PhSiH$_3$ formed PhH$_2$Si capped polyethylene(M_n=9.8 x10^4, Mw/M_n=1.8), and the copolymerization of ethylene with 1-hexene or styrene gave PhH$_2$Si capped copolymer (comonomer content 60 and 26 mol%, respectively; M_n=3.7·10^3, Mw/M_n=2.9 for ethylene-1-hexene copolymer, M_n=3.3·10^3 for ethylene-styrene copolymer) [50].
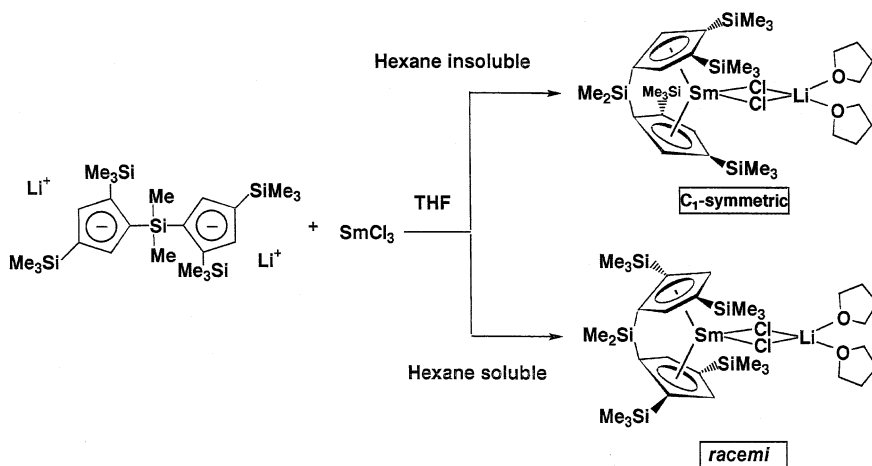

Fig. 17. Synthesis of organolanthanide(III) for polymerization of ethylene

Table 7. Ethylene polymerization by organolanthanide(III) complexes

Initiator	$M_n/10^4$	M_w/M_n	Activity (g/mol·h)
$(C_5Me_5)_2SmCH(SiMe_3)_2$			no polymerization
$SiMe_2[2,4-(SiMe_3)_2C_5H_2]_2SmCH(SiMe_3)_2$ (*racemic*)			no polymerization
$SiMe_2(Me_2SiOSiMe_2)(3-SiMe_3-C_5H_2)YCH(SiMe_3)_2$ (*meso*)			no polymerization
$SiMe_2[2(3),4-(SiMe_3)_2C_5H_2]_2SmCH(SiMe_3)_2$ (C_1)	41.3	2.19	$3.3 \cdot 10^4$
$SiMe_2[2(3),4-(SiMe_3)_2C_5H_2]_2YCH(SiM_3)_2$ (C_1)	33.1	1.65	$18.8 \cdot 10^4$

Initiator concentration, 0.2 mol%. Ethylene was introduced by bubbling at atmospheric pressure.
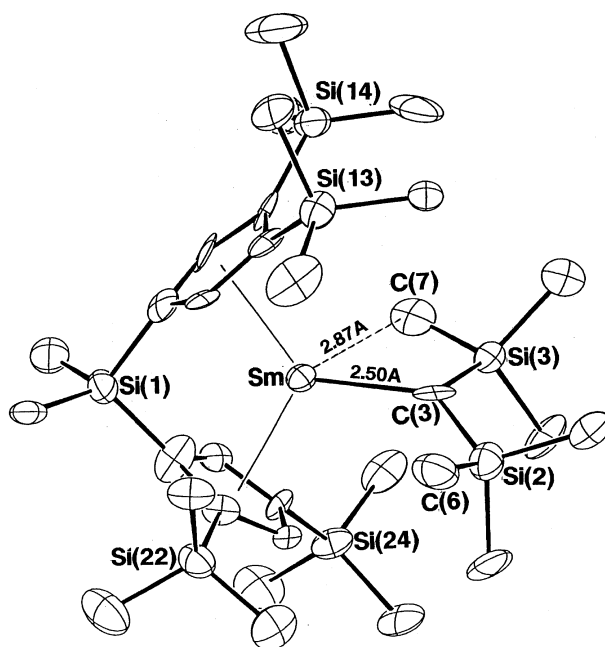
Fig. 18. X-ray structure of C_1 symmetric $SiMe_2[2(3),4-(SiMe_3)_2C_5H_2]_2SmCH(SiMe_3)_2$

Racemic, meso, and C_1 symmetric divalent organolanthanide complexes can be synthesized by allowing the dipotassium salt of the corresponding ligand to react with SmI_2 [51]. Figure 20 shows their structures determined by [1]H NMR and X-ray analyses. Table 8 shows the results of the ethylene polymerization with divalent samarium complexes. It is seen that the *meso* type complex has the
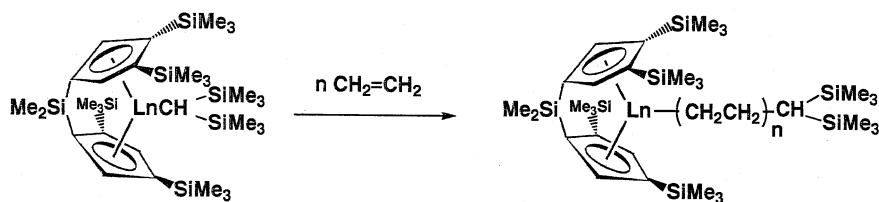
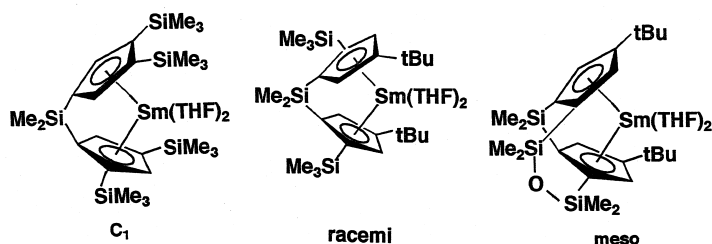**Fig. 19.** Initiation mechanism for polymerization of ethylene catalyzed by rare earth metal (III) complexes

Fig. 20. X-ray and NMR analysis of racemic, meso and C_1 symmetric complexes(II)
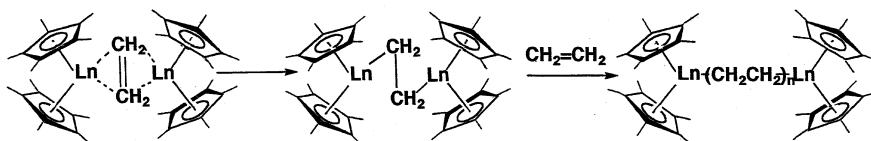

Fig. 21. Initiation mechanism for polymerization of ethylene catalyzed by rare earth meta (II) complexes

highest activity for the polymerization of ethylene, but the molecular weights of the resulting polymers are the lowest. On the other hand, the *racemic* and C_1 symmetric complexes produce much higher molecular weight polyethylene but the activity is rather low.

Particularly, the very high molecular weight polyethylene ($M_n > 100 \cdot 10^4$) obtained with C_1 complex deserves attention (Fig. 21). For the polymerization of α-olefins, only the *racemic* divalent complex showed good activity at 0 °C in toluene: poly(1-hexene) $M_n = 24,600$, $M_w/M_n = 1.85$; poly(1-pentene) $M_n = 8,700$, $M_w/M_n = 1.58$. Thus, we see that the reactivity of divalent organolanthanide complexes varies depending on their structure. The poly(1-alkene) obtained revealed highly isotactic structure (>95%) when examined by ^{13}C NMR (Fig. 22). The dihedral angles of Cp'-Ln-Cp' of racemic and meso type divalent complexes were 117 and 116.7°, respectively. These values are much smaller than those of

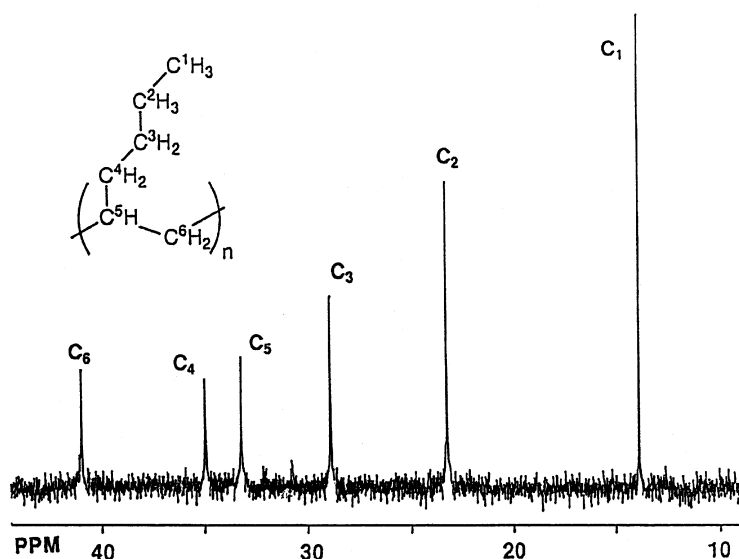**Fig. 22.** ^{13}C NMR spectrum of isotactic poly(1-hexene)

Table 8. Ethylene polymerization by divalent samarium complexes

Initiator	Time min	$M_n/10^4$	M_w/M_n	Activity (g/mol·h)
$(C_5Me_5)_2Sm(THF)_2$	1	2.28	1.25	43
		2.46	2.28	41
Racemic	1	11.59	1.43	6
		35.63	1.60	14
Meso	5	1.94	3.29	14
		4.73	3.49	47
C_1 Symmetry	5	100.8	1.60	1.6
		>100.0	1.64	1.1

Sm(C_5Me_5)$_2$(THF) (136.7°) [52] and Sm(C_5Me_5)$_2$ (140.1°) [53]. Therefore, it can be concluded that the complexes having smaller Cp'-Ln-Cp' angles are more active for the polymerization of ethylene and α–olefins.

More recently, YR$_2$[tris(pyrazoyl)borate] of trivalent state was found to have excellent activity for the polymerization of ethylene (Fig. 23). When R is C_6H_5, resulting M_w reaches $1.2 \cdot 10^6$ (M_w/M_n=4.10). However, the present initiator is inactive for the polymerization of 1-olefins such as propylene and 1-hexene [54].
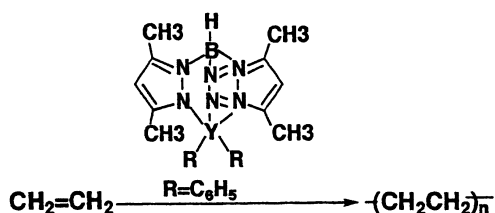
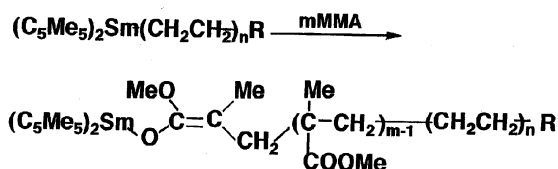Fig. 23. YR$_2$[tris(pyrazoyl)borate] initiated polymerization of ethylene

Fig. 24. Block copolymerizations of ethylene with MMA

10
Block Copolymerization of Ethylene with Polar Monomers

Block copolymerization of ethylene or propylene with polar monomers is yet to be attained in polyolefin engineering. The success of this type of block copolymerization should give hydrophobic polymeric materials having remarkably high adhesive, dyeing, and moisture adsorbing properties. The following is the first example of a well-controlled block copolymerization using the unique dual catalytic function of LnR(C$_5$Me$_5$)$_2$ (Ln=Sm, Yb, and Lu; R=H, Me) complexes toward polar and nonpolar olefins [55]. Ethylene was copolymerized with MMA first by the homopolymerization of ethylene (17–20 mmol) with SmMe(C$_5$Me$_5$)$_2$(THF) or [SmH(C$_5$Me$_5$)$_2$]$_2$(0.05 mmol) at 20 °C in toluene under atmospheric pressure, and then sequential addition of MMA (10 mmol) (Table 9). The initial step proceeded very rapidly, completed in 2 min, and gave a polymer of M_n=ca. 10,100 and M_w/M_n=1.42–1.44. However, the second step was rather slow, with the reaction taking 2 h at 20 °C (Fig. 24). The polymer obtained was soluble in 1,2-dichlorobenzene and 1,2,4-trichlorobenzene at 100 °C but insoluble in THF and CHCl$_3$. This fact indicates quantitative conversion to the desired linear block copolymer. Repeated fractionation in hot THF did not change the molar ratio of the polyethylene and poly(MMA) blocks, though poly(MMA) blended with polyethylene can easily be extracted with THF. With the copolymerization, the elution maximum in GPC shifted to a higher molecular

Table 9. Block copolymerization of ethylene with polar monomers

Polar monomer	Polyethylene block[a]		Polar polymer block[b]		Unit ratio
	$M_n/10^3$	M_w/M_n	$M_n/10^3$	M_w/M_n	
MMA	10.3	1.42	24.2	1.37	100:103
		1.39	12.8	1.37	100:13
MeA	6.6	1.40	15.0	1.36	100:71
		2.01	3.0	1.66	100:4
EtA	10.1	1.44	30.8	2.74	100:85
		1.97	18.2	3.84	100:21
VL	10.1	1.44	7.4	1.45	100:20
CL	6.6	1.40	23.9	1.76	100:89

[a] Determined by GPC using standard polystyrene
[b] Determined by ^{1}H NMR
Polymerization was carried out at 0 °C.

weight region, with its initial unimodal pattern unchanged. The relative molar ratio of the polyethylene and poly(MMA) blocks was controllable at will in the range of 100:1 to 100:103 if the M_n of the initial polyethylene was fixed to ca. 10,300. ^{1}H and ^{13}C NMR spectra for the copolymers as well as their IR absorption spectra were superimposable onto those of the physical mixtures of the respective homopolymers. The molar ratio of the poly(MMA) and polyethylene blocks, however, decreased as the M_n of the prepolymer increased, especially when M_n exceeds over ca. 12,000 at which value polyethylene began precipitating as fine colorless particles. It is noteworthy that smooth block copolymerization of ethyl acrylate or methyl acrylate to the polyethylene growing chain (M_n=6600–24,800) can be realized by the sequential addition of the two monomers.

We have extended the above work to the block copolymerization of ethylene with lactones. δ-Valerolactone and ε-caprolactone were incorporated to the growing polyethylene end at ambient temperature and the expected AB type copolymers (100:1 to 100:89) were obtained in high yield.

The treatment of the resulting block copoly(ethylene/MMA) (100:3, M_n= 35,000) and block copoly(ethylene/ε–caprolactone) (100:11, M_n=12,000) with dispersed dyes (Dianix AC-E) made them deeply dye with three primary colors, though polyethylene itself was inert to these dyes. Reversed addition of the monomers (first MMA or lactones and then ethylene) induced no block copolymerization at all, even in the presence of excess ethylene, and only homo-poly(MMA) and homo-poly(lactone) were produced. Hence, these copolymers can be said to have a very desirable chemical reactivity.

More recently, Yang et al. [56] have examined a new approach in which a reactive functional group was introduced into polyolefins using methylenecyclopropane. Thus, ethylene (1.0 atm) was copolymerized with methylenecyclopropane (0.25–2.5 ml) using $[LnH(C_5Me_5)_2]_2$ (Ln=Sm, Lu) in toluene at 25 °C, and it was shown that 10–65 of exo-methylenes were incorporated per 1000 -CH$_2$- units. The resulting polymer had a M_w of 66–92·10^3. Yet its M_w/M_n was larger than 4.
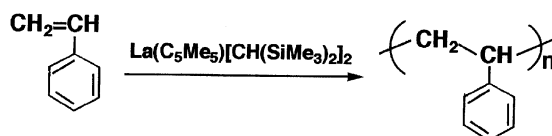
Fig. 25. Styrene polymerization by La(C$_5$Me$_5$)[CH(SiMe$_3$)$_2$]$_2$

11
Polymerization of Styrene

Styrene polymerization was performed by using binary initiator systems such as Nd(acac)$_3$/AlR$_3$ or Nd(P$_{507}$)$_3$/AlR$_3$. *Syndio*-rich polystyrene was obtained at a ratio of Al/Nd=10–12 [57]. More recently, it was shown that the Gd(OCOR)$_3$/iBu$_3$Al/Et$_2$AlCl catalytic system initiates the copolymerization of styrene with butadiene, but gives only atactic polystyrene [58]. The Sm(OiPr)$_3$/AlR$_3$ or Sm(OiPr)$_3$/AlR$_2$Cl (Sm/Al=1–15) catalytic system also initiates the polymerization of styrene to give a high molecular weight polymer (M_n= 300,000), low in polydispersity but atactic in stereoregularity [59]. The cationic polymerization of styrene using Ln(CH$_3$CN)$_9$(AlCl$_4$)$_3$(CH$_3$CN) was also examined [60], with the finding that the activity increased in the order La (conversion 73%)>Tb=Ho>Pr=Gd>Nd>Sm=Yb>Eu (conversion 54%), while M_n decreased with increasing the polymerization temperature from 0 (20· 10^3) to 60 °C (13· 10^3). A more recent study showed that the single component initiator [(tBuCp)$_2$LnCH$_3$]$_2$ (Ln=Pr, Nd, Gd) initiated the polymerization of styrene at relatively high temperature, 70 °C, with a conversion of 96% and the M_n of 3.3· 10^4 for [(tBuCp)$_2$NdCH$_3$]$_2$ [61], though stereoregularity was very poor. The activity varied greatly with the lanthanide element; and catalytic activity increased in the order Nd>Pr>Gd>>Sm=Y (the Sm and Y complexes showed practically no activity). Therefore, the reaction is supposed to follow the radical initiation mechanism. Styrene polymerization was also performed successfully using the single component initiators, [(Me$_3$Si)$_2$N]$_2$Sm(THF)$_2$, [(Me$_3$Si)$_2$CH]$_3$Sm, and La(C$_5$Me$_5$)[CH(SiMe$_3$)$_2$]$_2$(THF) at 50 °C in toluene without addition of any cocatalyst (Fig. 25). The resulting polymers had M_n=1.5–1.8· 10^4 and M_w/M_n=1.5–1.8, and show atactic properties [62].

Thus no success has yet been achieved in synthesizing syndiotactic polystyrene with rare earth metal complexes, in contrast to the synthesis of highly syndiotactic polystyrene with TiCl$_3$(C$_5$Me$_5$)/(AlMe-O-)$_n$ (syndiotacticity >95%) [63,64].

12
Stereospecific Polymerization of Conjugated Dienes

Organolanthanide(III) based binary initiator systems were used by Yu et al. [65] for stereospecific polymerization of butadiene and isoprene. Typically, the po-

lymerization of butadiene catalyzed by $C_5H_5LnCl_2 \cdot THF/AlR_3$ yielded polymers with a *cis*-1,4-content as high as 98% (Fig. 26). The polymerization activity decreased in the order Nd>Pr>Y>Ce>Gd and $iBu_2AlH>iBu_3Al>Et_3Al>Me_3Al$, while the viscosity of the polymer decreased in the order $Et_3Al>iBu_3Al>$ iBu_2AlH. Although the $NdCl_3/iBu_3Al$ system exhibited practically no initiating activity, the use of $NdCl_3/PrOH$ instead of the solvent-free metal chloride brought about high polymerization activity and high stereoregularity in the *cis*-1,4-polymerization of butadiene [66]. The M_n of the polymer increased linearly with increasing conversion and reached $1530 \cdot 10^3$ at 85% conversion when $NdCl_3 \cdot iPrOH/AlEt_3$ (1:10) was used in heptane at –70 °C, but M_w/M_n (1.8–2.5) showed no change with conversion. The number N of polymer chains per metal atom was 1.09–1.43 at –70 °C, and increased to 2.0–3.0 when the polymerization temperature was raised to 0 °C. Most noteworthy is a very high *cis*-content realized at –70 °C, which amounted to 99.4%.

This indicates the existence of the anti-π-allyl-Nd species rather than the syn-π-allyl-Nd species in the polymerization system. The *cis*-1,4-content of poly(butadiene) increased as the $AlEt_3$ concentration was lowered [66].

The arene organolanthanide system, $Nd(C_6H_6)(AlCl_4)_3/AliBu_3$ (Al/Nd=30), also induces the catalytic polymerization of isoprene to give *cis*–1,4 polymers in 92–93% selectivity at low conversion (17–36%). Neither of the $Nd(C_6Me_6)(AlCl_4)_3/AliBu_3$ (1:30) nor $NdCl_3/AlCl_3/AliBu_3$ (1:3:30) systems showed catalytic activity for the polymerization of isoprene [67]. The random copolymerization of isoprene with butadiene went smoothly with the use of the $Nd(C_6H_6)(AlCl_4)_3/AliBu_3$ system and gave an isoprene/butadiene(1:4) copolymer at high yield, but no data for Mw/Mn and Mn were reported [68]. The $(\beta\text{-}CH_3\text{-}\pi\text{-allyl})_2LnCl_5Mg_2(TMEDA)_2/AlR_3$ and $(allyl)_4LnLi$ systems also initiate the 1,4-polymerization of isoprene in 50% stereoregularity at high conversion. Highly selective *cis*-1,4-polymerizations of conjugated dienes were obtained by the use of homogeneous $(CF_3COO)_2NdC1 \cdot EtOH/AlEt_3$ (1:7) initiator
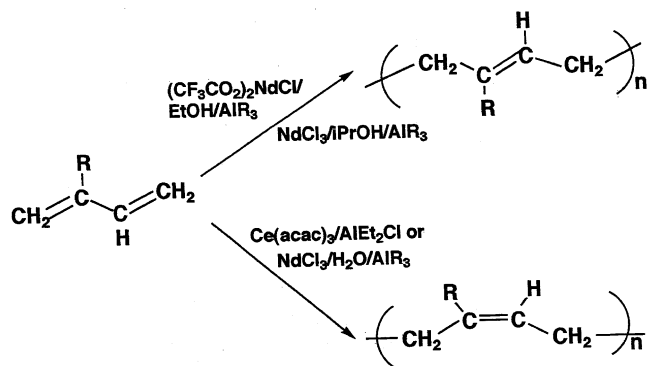

Fig. 26. Rare earth metal initiated polymerizations of conjugated dienes

system, i.e. 97.5% *cis*-selectivity for butadiene and 96.7% for isoprene. Although bimetallic species like $(CF_3COO)EtNd(\mu\text{-}Cl)(\mu\text{-}H)AlEt_2$ are proposed as active one, their exact structures are still unknown [69]. The molecular structure of dimer complexes, $[(CF_3C)(\mu^2\text{-}O)_2(\mu^3\text{-}O)_4YAlEt_2(THF_2)]_2$ and $[(CF_3)(\mu^2\text{-}O)_3(\mu^3\text{-}O)_3NdAlEt_2(THF_2)]_2$, generated during the reaction between $(CF_3COO)_2NdC1$ and $AlEt_3$, has recently been elucidated by X-ray analysis. However, these complexes are considered to be byproducts because they give polymers of low stereoregularity only at low yield [70].

A remarkable solvent effect was observed on the activity of the Nd $(OCOC_7H_{15})_3/Et_2AlCl/iBu_3Al$ system, which initiates the *cis*-1,4-polymerization of butadiene (>98%) and isoprene (>95%). Aliphatic compounds such as pentane, 1-pentene, and 2-pentene behave as good solvents, while aromatic compounds such as toluene and mesitylene act as inhibitors [71]. The coordination of aromatic compounds to the metal center may be responsible for the remarkable suppression of the polymerization, as was the case in the polymerization using cobalt catalysts [72]. A binary initiator system, $LnCl_3[(BuO)_3PO]_3/AliBu_3$, and a ternary system, $Ln(naphthenate)_3/AliBu_3/Al_2Et_3Cl_3$ (naphthenate; $C_{10}H_7COO$), also behave as good initiators for the *cis*-1,4-polymerization of isoprene [73]. In both cases, the polymerization activity varies with the nature of the metal in the order Nd>Pr>Ce>Gd>La>>Sm>Eu. Thus, the activity increases with increasing electronegativity and does so with decreasing M^{3+} ionic radius, except for Sm^{3+} and Eu^{3+} which can be easily converted to the M^{2+} species in the presence of a reducing agent. No relationship was observed between the initiating activity and the Ln-O or Ln-Cl bond energy determined by IR and laser Raman spectroscopy.

Block copolymerization of butadiene with isoprene (32:68–67:33) giving high *cis*-1,4-polymers have also been successfully made with the Ln(naphthenate)$_3$/AliBu$_3$/Al$_2$Et$_3$Cl$_3$ system at temperature –78 to 33 °C. Noteworthy is the relatively long life time of this initiator. Thus, it was possible to copolymerize isoprene 1752 h after the polymerization of butadiene. The $(iPrO)_2HLn_2Cl_3HAlEt_2$ species (Ln=Gd, Dy, Er, Tm) [74] prepared from either Ln(iPrO)$_3$/Et$_2$AlCl/Et$_3$Al or (iPrO)$_2$LnCl/Et$_3$Al also can initiate the *cis*-1,4-polymerization of butadiene and isoprene. The most probable structure of this complex as evidenced by X-ray analysisis is (iPrO)HLnEt(Cl)AlHEt(Cl)LnCl(OiPr). The polymerization activity decreased in the order Gd>Dy>Er>Tm and the *cis*-content ranged from 92 to 95% in the case of Gd derivatives. Random copolymerization of butadiene with isoprene was also performed using $Nd(C_6H_6)(AlCl_4)_3/AlR_3$ (Al/Nd=30) in benzene. Both monomers were incorporated in the copolymer selectively with *cis*–1,4-butadiene 96.1–96.4% and *cis*–1,4-isoprene 97.5–98.3%. The conversion increased with increase in the polymerization temperature from 0 (10%) to 80 °C (80–100%) [75].

Some rare earth metal based initiators induce the *trans*-1,4-polymerization of conjugated dienes at high yield. The Ce(acac)$_3$/AlEt$_2$Cl system as well as the CeCl$_3$/AlEt$_2$Cl and GdCl$_3$/AlEt$_3$ systems were most effective catalyst system to carry out this type of polymerization for isoprene with high selectivity (91–

97%) [76]. The marked difference in the selectivity between the $Ce(acac)_3/AlEt_3$ and the $C_5H_5LnCl_2/AlR_3$ or $(iPrO)_2LnCl/AlR_3$ initiator systems may be due to a specific action of small amounts of water present in the system. Actually, metal compound hydrates like $NdCl_3 \cdot 6H_2O$, $PrCl_3 \cdot 6H_2O$ and $UO_2(C_2H_3O_2)_2 \cdot 6H_2O$ can initiate the *trans*-polymerization in the presence of AlR_3 [77]. Prolonged aging of the initiator system decreased the activity significantly, presumably owing to an irreversible self-reaction of the intermediate generated from the organolanthanide and water. A precise recent study on the effect of water has revealed that a maximum conversion was attainable at an $H_2O/AlEt_2Cl$ ratio of 1.1–1.2, which produces $(AlEt-O-)_n(AlCl-O)_m$ species. However, the molecular weight was independent of the amount of water added to $AlEt_2Cl$.

Butadiene-styrene copolymerization was attempted using the $L_3Ln-RX-AlR_3$ system [78]. Especially, $(CF_3COO)_3Nd/C_5H_{11}Br/AliBu_3$ (1:3:15) was found to be active for this type of copolymerization, with the *cis*-content of butadiene unit amounting 97.8% and the styrene content to ca. 32%. However, for the system of isoprene/styrene, the *trans*-1,4-polyisoprene copolymer was produced exclusively.

13
Stereospecific Polymerization of Acetylene Derivatives

Polyacetylene (PA) is one of the simplest conjugated polymers, useful for manufacturing lightweight high energy density plastics for storage batteries, solar energy cells, etc. Acetylene can be polymerized to give high *cis* PA film with $Ti(OiBu)_4/AlEt_3$ [79] or $Co(NO_3)_2/NaBH_4$ [80] at temperatures lower than –78 °C. Recently, it has been reported that $Ln(naphthenate)_3/AlR_3/Donor$ (1:10:2–3) (Donor=acetone, ether, ethyl acetate) systems also can initiate stereoregular *cis* polymerization of acetylene at 30 °C, which leads to silvery metallic film [81, 82]. The polymer yield increased with increasing polymerization temperature from –15 to 45 °C. A *cis*-polyacetylene with 95% selectivity was obtained when the Al/Ln ratio was adjusted to ca. 5. The polymerization activity decreased in the order Y=Ce>Nd=Tb>Pr>La>Lu>Gd>Tm=Er>Ho=Yb=Eu>Sm>Dy. The *trans* content of the film amounted to 100% when the temperature was raised to 180 °C. The elements leading to PA film with a *cis* content exceeding 95% are La, Pr, Nd, Sm, Gd, Tb, Dy, Ho, Er, Tm, and Y. The electrical conductivity of the films was $294 \cdot 10^{-8}$ Scm^{-1} for La, $181 \cdot 10^{-8}$ Scm^{-1} for Nd, $194 \cdot 10^{-8}$ Scm^{-1} for Gd, $490 \cdot 10^{-8}$ Scm^{-1} for Tb, and $184 \cdot 10^{-8}$ Scm^{-1} for Tm. Differential scanning calorimetry revealed two exothermic peaks at 200 and 380 °C and an endothermic peak at 460 °C. These peaks were attributed to *cis-trans* isomerization, hydrogen migration, and chain decomposition, respectively [82].

$Sc(naphthenate)_3/ROH/AlR_3$ (1/2/7) has been found to exhibit an activity similar to the lanthanide series catalyst [83] (Fig. 27). The *cis* PA film obtained with it showed an electrical conductivity of 14.4 Scm^{-1} when the polymer was doped with I_2 at a ratio of $(CHI_{0.04})_n$, and the TEM measurement suggested the formation of fibrils of about 20–30 nm in size.

The $(P_{204})_3Ln/AlR_3$ system also exhibited good activity for the polymerization of acetylene when Al/Ln ratio was 5 [83]. The polymerization was conducted by the conventional method, and polymers with silver metallic appearance were obtained. The addition of an oxygen-containing donor was effective for enhancing the polymerization rate and the *cis*-content. The effects were especially marked for P_{204} (PO/Nd=1.1). The activity decreased in the order Nd= Tb>Ce>Pr=Y>La>Er>Ho>Sm=Eu>Yb=Lu>Gd>Tm>Dy and the *cis*-content decreased in the order Pr (95%)>Lu=Tb=Dy (92%)>Er=Y=Sm=Gd (87–89%). The polymerization activities of $Nd(P_{507})_3$, $Nd(P_{204})_3$, and $Nd(P_{215})$ were compared and found to increase in this order, the result is consistent with the basicities of the ligands ($P_{507}H$=pKa 4.10, $P_{204}H$=pKa 3.32, $P_{215}H$=pKa 3.22). The M-C bond is supposed to weaken as the electron donating ability of the ligand increases. The $Nd(iPrO)_3/AlEt_3$ (Al/Nd=10) system [84] was also shown to be a good initiator for the polymerization of acetylene. The soluble fraction obtained was considered to be *trans*-polyacetylene, which was shown to have a molecular weight of 277–540. Its ^1H NMR spectrum revealed methyl groups at δ= 0.826 ppm and terminal vinyl groups at 4.95 ppm.

Phenylacetylene was polymerized to give a polymer of high *cis* configuration by the use of the Ln(naphthenate)$_3$/AlEt$_3$ system [85, 86], with the activity decreasing in the order Gd>Lu>Nd=Ce>Ho>Sm>Dy=Eu>Er>Pr>La>Y=Tm>Yb, and the *cis*-content exceeding 90%. It had M_n and M_w of $2 \cdot 10^5$ and $4 \cdot 10^5$, respectively, and was crystalline according to XRD and SEM measurement. Its softening point was in the range 215–230 °C. Other terminal alkynes such as 1-hexyne, 1-pentyne, 3-methyl-1-pentyne, 4-methyl-1-pentyne, 3-methyl-1-butyne, and phenylacetylene were found to polymerize quantitatively in the *cis*-fashion with the Ln(naphthenate)$_3$/AlR$_3$/C$_2$H$_5$OH (Ln=Sc, Nd) or Ln(P$_{204}$)$_3$/ AlR$_3$/C$_2$H$_5$OH (1:7:3) system. The highest molecular M_n obtained was $16.8 \cdot 10^4$ for poly(1-pentyne). Trimethylsilylacetylene was oligomerized to H(Me$_3$SiC=CH)$_n$CH$_2$CHMe$_2$ (n=2–3) by the use of LnX$_3$(Donor)/AliBu$_3$ (Ln=Gd, Pr, Nd, Tb, Dy, Lu; X=Cl, Br) [87, 88]. The catalytic dimerization of terminal alkynes using (C$_5$Me$_5$)$_2$LnCH(SiMe$_3$)$_2$ (Ln=Y, La, Ce) has been reported recently. Here the dimer was a mixture of 2,4-disubstituted 1-buten-3-yne and 1,4-disubstituted 1-
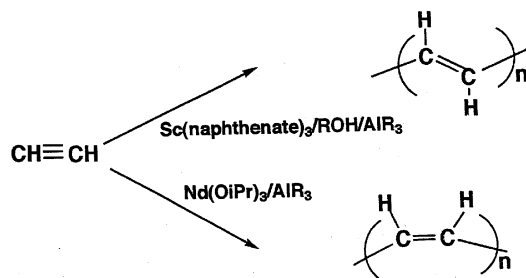

Fig. 27. Rare earth metal initiated polymerizations of acetylene derivatives

buten-3-yne for phenylacetylene and (trimethylsilyl)acetylene, but it was a 2,4-disubstituted dimer for alkylacetylene [89]. Selective formation of 2,4-disubstituted 1-buten-3-ynes has already been achieved with the $(C_5Me_5)_2TiCl_2$/RMgX catalyst [90].

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Polymer-Supported Rare Earth Catalysts Used in Organic Synthesis

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Abstract. Three types of polymer-supported rare earth catalysts, Nafion-based rare earth catalysts, polyacrylonitrile-based rare earth catalysts, and microencapsulated Lewis acids, are discussed. Use of polymer-supported catalysts offers several advantages in preparative procedures such as simplification of product work-up, separation, and isolation, as well as the reuse of the catalyst including flow reaction systems leading to economical automation processes. Although the use of immobilized homogeneous catalysts is of continuing interest, few successful examples are known for polymer-supported Lewis acids. The unique characteristics of rare earth Lewis acids have been utilized, and efficient polymer-supported Lewis acids, which combine the advantages of immobilized catalysis and Lewis acid-mediated reactions, have been developed.

Keywords: Lewis acids, Polymer-supported catalysts, Rare earth triflate, Combinatorial synthesis, Carbon–carbon bond-forming reactions

1
Introduction

Use of polymer-supported catalysts offers several advantages in preparative procedures. Simplification of product work-up, separation, and isolation as well as reuse of the catalyst including use of flow reaction systems could lead to economical automation processes. Although the use of immobilized homogeneous catalysts is of continuing interest [1], few successful examples are known for polymer-supported Lewis acids [2,3]. This is probably due to the instability of most Lewis acids to air (moisture) and water. During preparation of polymer-supported catalysts, many manipulations have to be carried out in air or in the presence of water. On the other hand, it was recently found that some rare earth Lewis acids are stable in water [4]. Utilizing this very unique characteristic, several efforts to develop efficient polymer-supported Lewis acids combining the advantages of immobilized catalysis and Lewis acid-mediated reactions, have

been made. In this chapter, three types of polymer-supported rare earth catalysts, Nafion-based rare earth catalysts, polyacrylonitrile-based rare earth catalysts, and microencapsulated Lewis acids are discussed [5].

2
Nafion-Based Rare Earth Catalysts

Recently, scandium triflate [Sc(OTf)$_3$] was found to be stable in water and successful Lewis acid catalysis was carried out in both water and organic solvents [6–8]. Sc(OTf)$_3$ coordinates to Lewis bases under equilibrium conditions, and thus activation of carbonyl compounds using a catalytic amount of the acid has been achieved [6,7]. In addition, effective activation of nitrogen-containing compounds such as imines, amino aldehydes, etc. has been performed successfully [8]. Encouraged by the characteristics and the usefulness of Sc(OTf)$_3$ as a Lewis acid catalyst, a polymer-supported scandium catalyst was prepared.

   Nafion (NR-50, Du Pont) was chosen as the supporting framework [9]. Three equivalents of Nafion were treated with ScCl$_3$·6H$_2$O in acetonitrile under reflux conditions [10]. After 40 h, 96% of the ScCl$_3$·6H$_2$O was consumed and the polymer thus prepared (Nafion-Sc) contained 1.3% Sc, according to ICP analysis. Choice of solvent is important at this stage; only 27% of the ScCl$_3$·6H$_2$O was consumed when 1,2-dichloroethane was used as the solvent. This Nafion-Sc catalyst was then tested in several synthetic reactions [11]. First, allylation reactions of carbonyl compounds were investigated. Allylation reactions of carbonyl compounds are among the most important carbon–carbon bond-forming reactions, and the products, homoallylic alcohols having hydroxyl and double bond groups, are synthetically useful intermediates [12]. Nafion-Sc was also found to be effective in the allylation reactions of carbonyl compounds with tetraallyltin, and selected examples are shown in Table 1 [13]. In all cases, the reactions proceeded smoothly in both organic and aqueous solvents to afford the desired homoallylic alcohols in high yields. Not only aldehydes, but also ketones worked well. Moreover, use of aqueous solvents enabled the reactions of non-protected carbohydrates [14]. Non-protected sugars reacted directly with tetraallyltin to give the adducts, which are useful intermediates for the synthesis of higher sugars. Salicylaldehyde and 2-pyridinecarboxaldehyde reacted with tetraallyltin to afford the corresponding homoallylic alcohols in good yields. These compounds are known to react with the Lewis acids rather than the nucleophile under general Lewis acidic conditions.

   Nafion-Sc was also found to be effective in some other reactions (Schemes 1–3). In typical Lewis acid-mediated reactions, such as Diels–Alder, Friedel–Crafts acylation, and imino Diels–Alder reactions, Nafion-Sc worked efficiently to afford the corresponding adducts in high yields.

   It was also found that Nafion-Sc could be easily recovered and reused. The catalyst was recovered simply by filtration and washing with a suitable solvent, and the activity of the recovered Nafion-Sc was comparable to the fresh catalyst; in the reaction of benzaldehyde with tetraallyltin in H$_2$O/MeOH/toluene(1:7:4)

Table 1. Sc-Nafion-catalyzed allylation reactions of carbonyl compounds with tetraallyltin[a]

| Carbonyl Compound	Product	Solvent[b]	Yield (%)
PhCHO	Ph, OH (homoallylic alcohol)	A / B / C	91 / 90 / 91
Ph–CH₂CH₂–CHO	Ph, OH	A / C	83 / 83
Ph–CH=CH–CHO	Ph, OH	A / C	93 / 98
pyridine-2-CHO	pyridine, OH	A	78
Ph–C(O)–CH₃	Ph, OH	A	57[c]
Ph–CH₂CH₂–C(O)–CH₃	Ph, OH	A / C	64[c] / 87[c]
Ph–CH=CH–C(O)–CH₃	Ph, OH	A / C	95[c] / 85[c]
Ph–C(O)–CO₂Me	MeO₂C OH, Ph	A / C	81[c] / 84[c]
D-arabinose	AcO···OAc OAc / OAc OAc	A	76[c,d,e]
D-ribose	AcO···OAc OAc / OAc OAc	A	91[c,d,f]
D-glucose	AcO···OAc OAc OAc / OAc OAc	A	64[c,d,g]

[a] The reaction was carried out at rt unless otherwise noted.
[b] A: H₂O/THF (1:9); B: H₂O/MeOH/toluene (1:7:4); C: CH₃CN.
[c] The reaction was carried out at 60 °C.
[d] The products were isolated after acetylation.
[e] *syn/anti*=59:41.
[f] *syn/anti*=65:35.
[g] Diastereomeric ratio=68:32. Relative configuration assignment was not made.
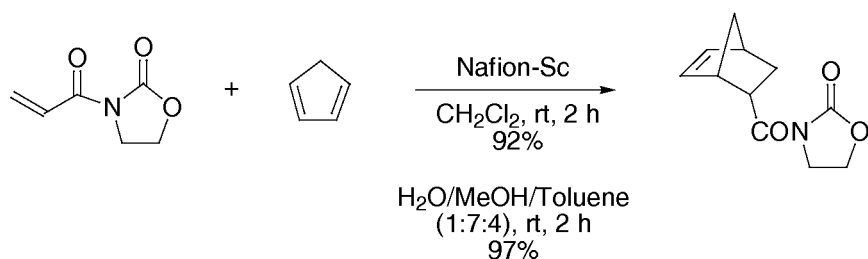
Scheme 1
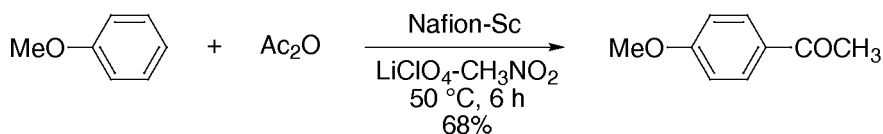
Scheme 2
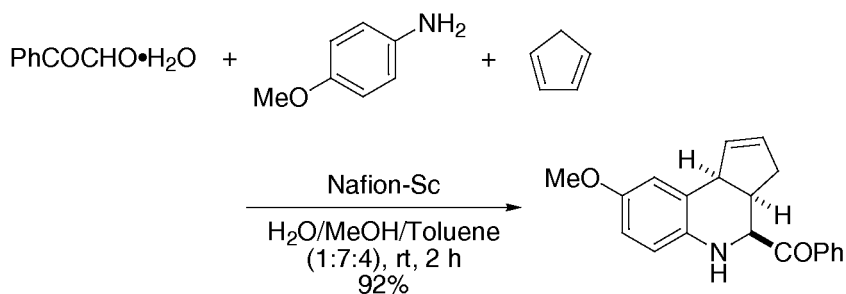
Scheme 3

[15] at rt; lst, 91% (15 h); 2nd, 81% (48 h); 3rd, 93% (40 h); in the reaction of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene at rt; 1st, 92% (2 h); 2nd, 87% (2 h); 3rd, 91% (2 h).

Nafion-Sc was also used in a flow system. Nafion-Sc was packed in a glass tube and substrates were passed through the column using a motor pump (Fig. 1) [16]. Results of the reaction of benzaldehyde with tetraallyltin in aqueous solution are shown in Scheme 4. It is noted that even higher yields were obtained in the 2nd, 3rd, and 4th runs than in the 1st run.
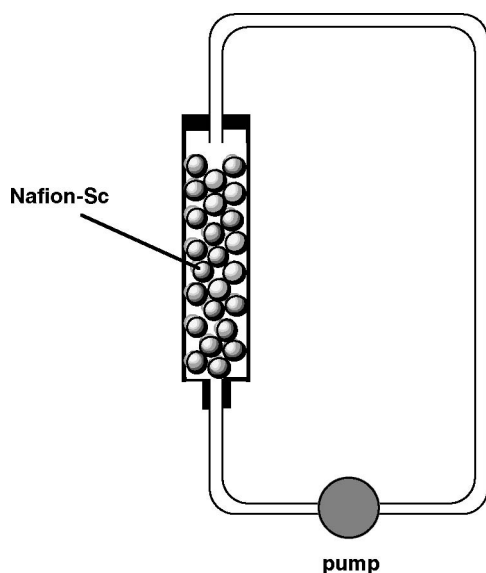
Fig. 1. A flow system using Nafion-Sc

Run	Yield (%)	Run	Yield (%)
1	75	3	84
2	93	4	84

Scheme 4. Nafion-Sc-catalyzed allylation using a flow system

3
Polyacrylonitrile-Based Rare Earth Catalysts

One of the drawbacks of polymer-supported catalysts is their low reactivity. Bearing in mind that the low reactivity might be ascribed to insolubility of the catalysts, a new polymer-supported catalyst, which was partially soluble in an appropriate solvent and is precipitated after completion of the reaction and recovered quantitatively by filtration, was searched. After several trials, a new scandium catalyst, polyallylscandium trifylamide ditriflate (PA-Sc-TAD), was finally developed. PA-Sc-TAD was readily prepared according to Scheme 5. Polyacrylonitrile was treated with $BH_3 \cdot SMe$ in diglyme for 36 h at 150 °C. The resulting amine (1) was reacted with Tf_2O in the presence of Et_3N in 1,2-dichlo-
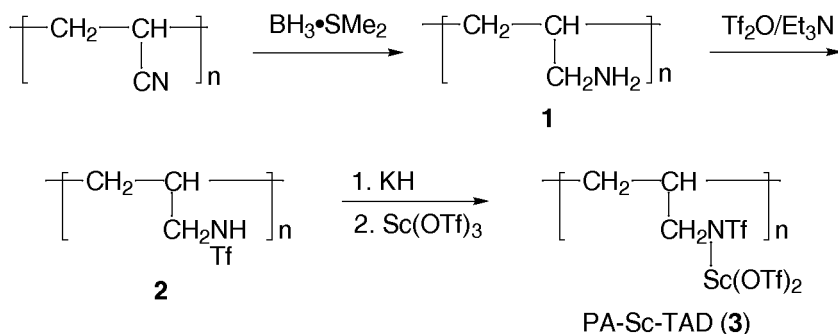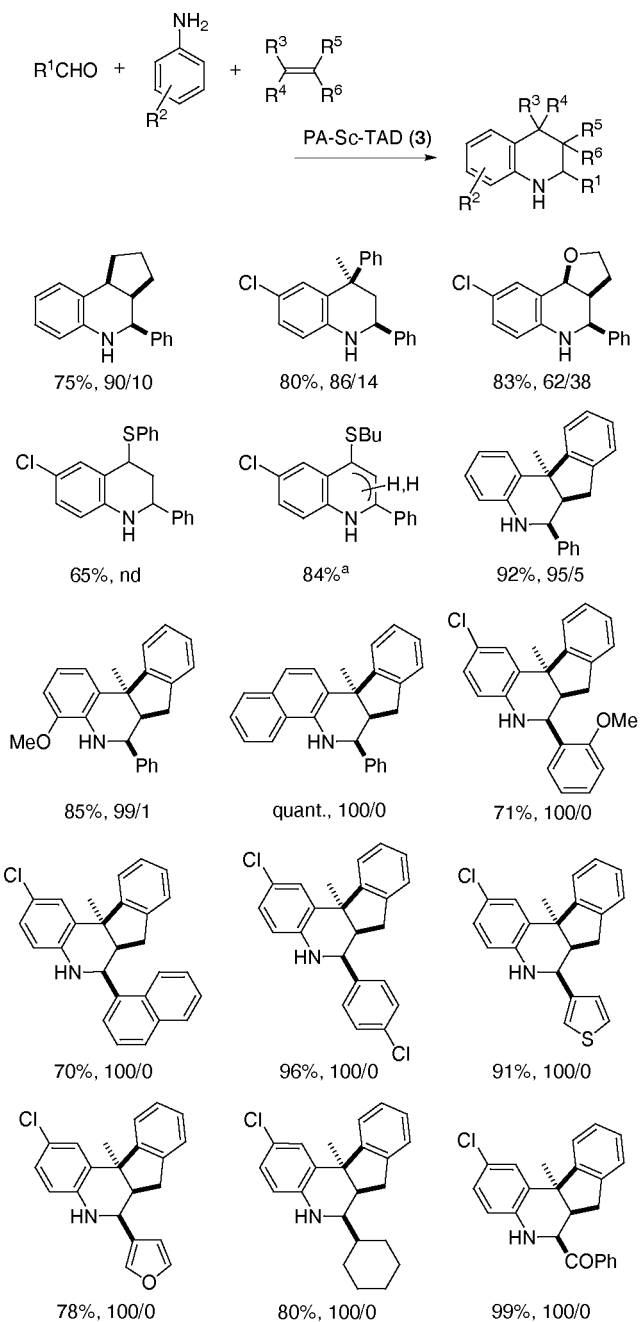
Scheme 5. Preparation of PA-Sc-TAD (3)

roethane for 10 h at 60 °C to afford sulfonamide **2** [17]. After compound **2** and KH were combined, Sc(OTf)$_3$ was added and the mixture was stirred in THF for 48 h at rt to give **3** [18]. PA-Sc-TAD (**3**) is gummy, but is dispersed and partially soluble in a mixture of CH$_2$Cl$_2$/CH$_3$CN. The dispersed catalyst assembles again when hexane is added.

In the presence of PA-Sc-TAD (**3**), quinoline synthesis based on a three-component coupling reaction [8b,c] was performed. An aldehyde, an aromatic amine, and an alkene were mixed in CH$_2$Cl$_2$/CH$_3$CN (2:1) at 60 °C for 12 h. Hexane was then added and the catalyst was filtered off. The filtrate was concentrated *in vacuo* to afford a crude adduct. After purification by column chromatography, the desired quinoline derivative was obtained in a high yield.
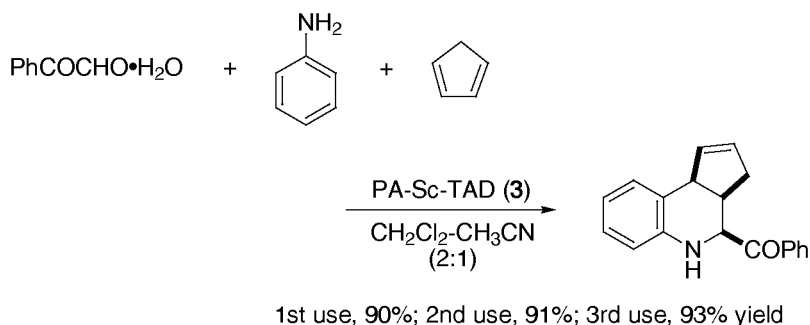
This method is especially useful for construction of a quinoline library (Scheme 6) [19]. The procedure is very simple; it involves just mixing the catalyst (PA-Sc-TAD), an aldehyde, an aromatic amine, and an alkene (alkyne). After filtration, the filtrates are concentrated to give almost pure quinoline derivatives in most cases. Dehydrating agents such as MS 4A, MgSO$_4$, etc. are not necessary. It is noted that PA-Sc-TAD is water-tolerant and that substrates having water of crystallization can be used directly. PA-Sc-TAD can be easily recovered and continuous use is possible without any loss of activity (Scheme 7).

Combinatorial synthesis, a synthetic strategy which leads to large chemical libraries, is beginning to make a significant impact especially on the drug discovery process. Although polymer-supported substrates (reagents) have often been employed for library construction [20], there are some disadvantages to this method. First, the reactions of polymer-supported reagents are sometimes slow, and differences in reactivity between the substrates lead to lack of diversity of the library in some cases. Secondly, the loading level of polymer-supported substrates is generally low (<0.8 mmol/g), and large-scale preparation is difficult. The present reactions using the polymer-supported catalysts provide a new method for synthesizing a large number of structurally distinct compounds. In addition, a characteristic feature of the present method compared with conventional combinatorial synthetic technology using polymer-supported reagents is
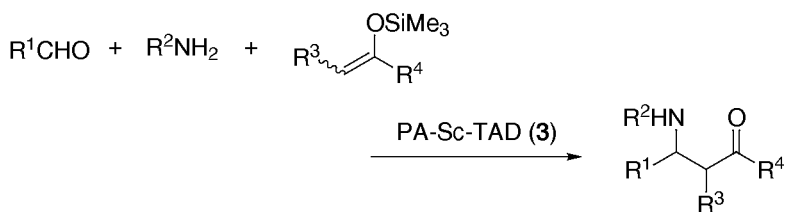
75%, 90/10

80%, 86/14

83%, 62/38

65%, nd

84%[a]

92%, 95/5

85%, 99/1

quant., 100/0

71%, 100/0

70%, 100/0

96%, 100/0

91%, 100/0

78%, 100/0

80%, 100/0

99%, 100/0

[a]Butyl ethynyl sulfide was used as a dienophile.

Scheme 6. Synthesis of quinoline derivatives

PhCOCHO•H$_2$O + [aniline NH$_2$] + [cyclopentadiene]

PA-Sc-TAD (3)
⟶
CH$_2$Cl$_2$-CH$_3$CN
(2:1)

[product structure] N–COPh
H

1st use, 90%; 2nd use, 91%; 3rd use, 93% yield

Scheme 7

that more than 100-mg scale syntheses with a large array of diverse molecular entries have been achieved with high purities (high yields and high selectivities). The number of commercially available aromatic aldehydes, aliphatic aldehydes, heterocyclic aldehydes, and glyoxals and glyoxylates that could be applicable to this synthesis is more than 200, and more than 200 aromatic amines and 50 alkenes (and alkynes) [21] are commercially available. Therefore, a quinoline library of more than a million compounds with high quantity and quality could be prepared by using an automation system based on this method. Moreover, the tetrahydroquinoline derivatives thus obtained are easily oxidized to dihydroquinoline or quinoline derivatives, which could double or triple the size of the library. Similarly, diverse amino ketone, amino ester, and amino nitrile derivatives were synthesized using PA-Sc-TAD as a catalyst (Schemes 8 and 9) [22].
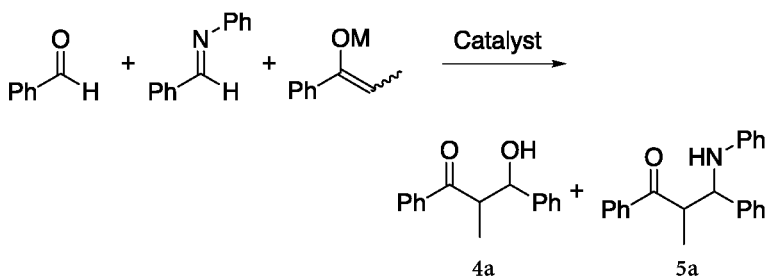
In addition to several advantages of polymer-supported catalysts in synthesis, such as simplification of reaction procedures, easy separation of catalysts and products, application to automation systems, etc., it is desirable to achieve high selectivities by utilizing the bulkiness of polymers, the stability of polymer-coordinated complexes, etc. [23]. Such examples have recently been reported using a polymer-supported scandium catalyst (PA-Sc-TAD) [24]. It is well recognized that aldimines are less reactive than aldehydes towards nucleophilic addition because of the difference in electronegativity between oxygen and nitrogen, the steric hindrance of aldimines, etc. [25]. In fact, in the model competition reaction of benzaldehyde and N-benzylideneaniline with propiophenone lithium enolate, the enolate attacks the aldehyde exclusively in the coexistence of the aldimine. On the other hand, it was recently reported that in the presence of a catalytic amount of Yb(OTf)$_3$, aldimines react with silyl enolates selectively to afford the corresponding adducts in high yields, even in the coexistence of aldehydes [26]. Scandium salts were then used in the same competition reactions. Although both scandium and ytterbium elements belong to group 3, the competition reaction of benzaldehyde and N-benzylideneaniline with the silyl enol ether of propiophenone in the presence of 20 mol% of Sc(OTf)$_3$ gave a mixture of aldehyde-adduct **4a** (13%) and aldimine-adduct **5a** (58%). Interestingly, when
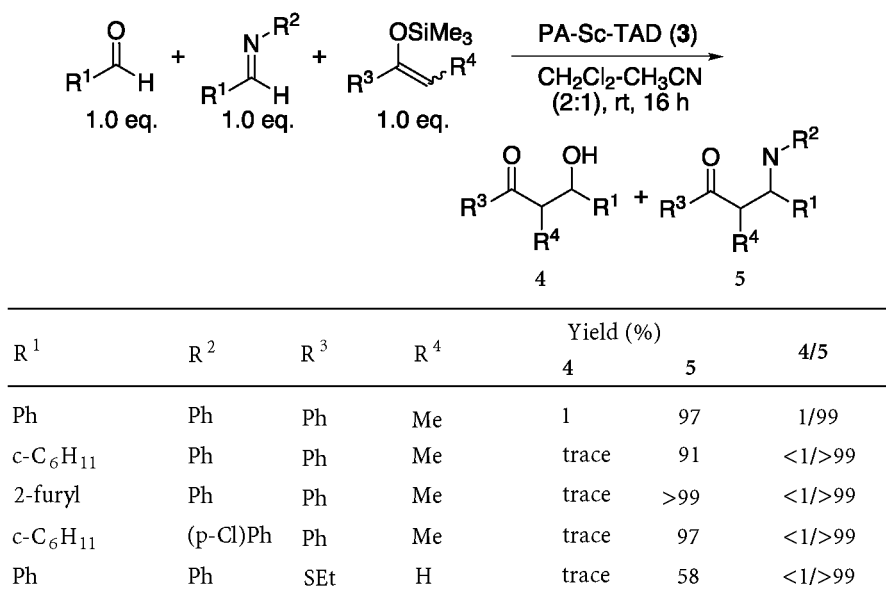
$$R^1CHO + R^2NH_2 + \underset{R^3}{\overset{OSiMe_3}{\diagdown}}R^4 \xrightarrow{\text{PA-Sc-TAD (3)}} \underset{R^1}{\overset{R^2HN}{\diagup}} \underset{R^3}{\overset{O}{\diagdown}}R^4$$

Scheme 8

$$R^1CHO + R^2NH_2 + Me_3SiCN \xrightarrow{\text{PA-Sc-TAD (3)}} \underset{R^1}{\overset{NHR^2}{\diagup}}CN$$
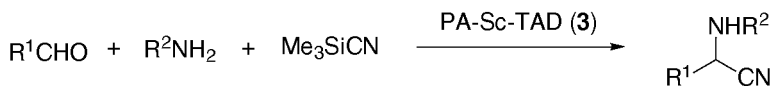
Scheme 9

M	Catalyst /equiv	Solvent /temp($^\circ$C)	Yield (%) 4a	5a	4a/5a
Li	——	THF/-78	97	trace	>99/1
TMS	Sc(OTf)$_3$/0.2	CH$_2$Cl$_2$/-23	13	58	18/82
TMS	PA-Sc-TAD/0.06	CH$_2$Cl$_2$:CH$_3$CN (2:1)/rt	1	95	1/99

Scheme 10. A competition reaction between an aldehyde and an aldimine

a polymer-supported scandium catalyst (PA-Sc-TAD) was used, the aldimine selectivity was improved dramatically, and the aldimine reacted with the silyl enolate to give the corresponding adduct in excellent selectivity (Scheme 10). Other combinations of aldehydes, aldimines, and silyl enolates were then tested, and the results are summarized in Scheme 11. In all cases, aldimines reacted with silyl enolates selectively in the coexistence of aldehydes to afford the corresponding adducts in high yields.

The unique selectivities obtained using the polymer-supported catalyst can be explained by the following equations. A catalytic amount of a scandium Lewis
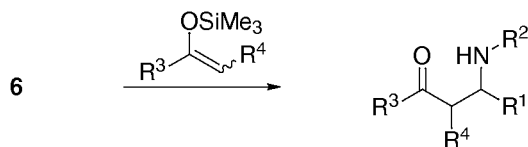
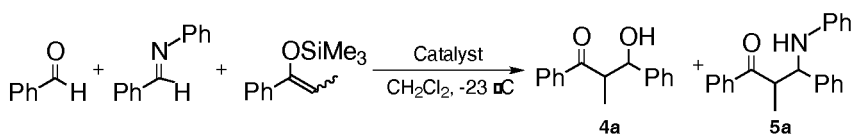**Scheme 11.** Aldimine-selective reaction using a polymer-supported catalyst

R^1	R^2	R^3	R^4	Yield (%) 4	Yield (%) 5	4/5
Ph	Ph	Ph	Me	1	97	1/99
c-C$_6$H$_{11}$	Ph	Ph	Me	trace	91	<1/>99
2-furyl	Ph	Ph	Me	trace	>99	<1/>99
c-C$_6$H$_{11}$	(p-Cl)Ph	Ph	Me	trace	97	<1/>99
Ph	Ph	SEt	H	trace	58	<1/>99
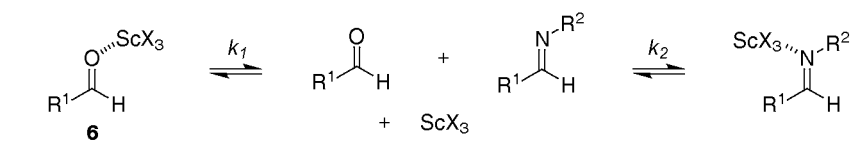
Scheme 12

Scheme 13

Scheme 14

Scheme 15

| Catalyst | Yield (%) | | 4a/5a |
	4a	5a	
$Sc(OTf)_3$	13	58	18/82
$Sc(OTf)_2(NTf_2)$	16	77	17/83
$Sc(NTf_2)_3$	3	77	4/96
$ScCl_3$	trace	43	<1/>99
$Sc(PF_6)_3$	2	76	3/97
$Sc(SbF_6)_3$	3	64	5/95
$Sc(AsF_6)_3$	26	49	35/65
$Sc(ClO_4)_3$	trace	87	<1/>99
$Sc(BPh_4)_3$	18	51	16/84
$\{[(3,5\text{-}CF_3)_2 Ph]_4 B\}_3 Sc$	10	66	13/87

acid first coordinates an aldimine, but the coordination occurs under equilibrium conditions (Schemes 12–14). Aldehyde/Lewis acid or aldimine/Lewis acid complexes should be stabilized by counter anions of scandium compounds (Scheme 15), and the ratios of 4/5 shown in Scheme 15 could depend on the stability of the complexes influenced by the counter anions. On the other hand, when the polymer-supported scandium catalyst (PA-Sc-TAD) was used, the catalyst also coordinated aldimines first. In this case, however, the aldimine/polymer-supported catalyst complexes are more stable than aldimine/*nonpolymer* Lewis acid complexes due to the *polymer effect*. Hence, the aldimines activated by the polymer-supported catalyst reacted with silyl enolates to afford aldimine adducts exclusively.

These aldimine-selective reactions using the polymer-supported catalyst will be applied to other nucleophilic addition reactions in organic chemistry.

4
A Microencapsulated Rare Earth Lewis Acid (A New Type of Polymer-Supported Catalyst)

In Sects. 1 and 2, polymer-supported scandium Lewis acids based on Nafion and a polyacrylonitrile derivative were discussed. While several useful reactions
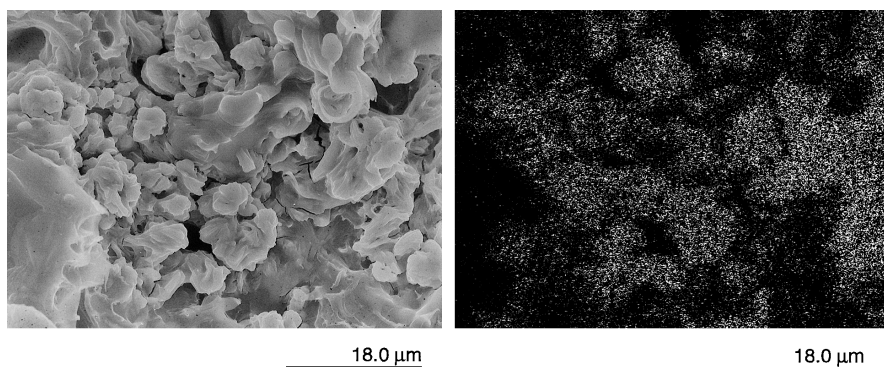
18.0 μm   18.0 μm

Fig. 2. Scanning electron microscopy (SEM) micrograph (*left*) and scandium energy dispersive X-ray (EDX) map of MC Sc(Otf)$_3$

have been developed, it was found that their reactivity, especially towards aldehydes and ketones, was lower than that of the nonpolymer Lewis acids. In general, catalysts are immobilized on polymers via coordinate bonds or covalent bonds. While the stability of polymer catalysts having coordinate bonds is often low, preparation of polymer catalysts having covalent bonds can be troublesome and their activities are generally lower than those of the nonpolymer catalysts [27]. As an unprecedented polymer-supported Lewis acid, attention is focused on a *microencapsulated* Lewis acid.

Microcapsules have been used for coating and isolating substances until such time as their activity is needed, and their application to medicine and pharmacy has been extensively studied [28]. Recently, much progress has been made in this field, and, for example, the size of the microcapsules that can be achieved has been reduced from a few μm to nanometers [28,29]. The idea is to apply this microencapsulation technique to the immobilization of Lewis acid catalysts onto polymers. That is, Lewis acids would be physically enveloped by polymer thin films and, at the same time, immobilized by the interaction between π electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbitals of the Lewis acids [30]. Sc(OTf)$_3$ was first chosen as a Lewis acid to be immobilized [31]. Preparation of the microencapsulated Sc(OTf)$_3$ [MC Sc(OTf)$_3$] was performed as follows: Polystyrene (1.000 g) was dissolved in cyclohexane (20 ml) at 40 °C, and to this solution was added Sc(OTf)$_3$ (0.200 g) as a core. The mixture was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coacervates were found to envelop the core dispersed in the medium, and hexane (30 ml) was added to harden the capsule walls. The mixture was stirred at rt for 1 h, and the capsules were washed with acetonitrile several times and dried at 50 °C [32,33]. A scanning electron microscopy (SEM) micrograph and a scandium energy dispersive X-ray (EDX) map of MC Sc(OTf)$_3$ prepared are shown in Fig. 2. It was found that small capsules of MC Sc(OTf)$_3$ adhered to each other, probably due to the small size of the core. Judging from the scandium mapping,
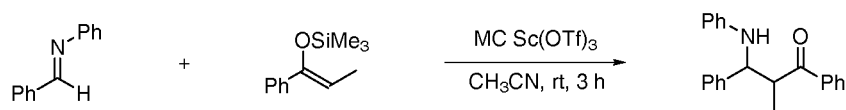
| Use [a]	Yield/%
1	90
2	90
3	88
4	89
5	89
6	88
7	90

[a] Recovered catalyst was used
  successfully (Runs 2,3,4...)

Scheme 16. Imino aldol reaction (flow system)

$Sc(OTf)_3$ was located *all over the polymer surface.* The importance of the benzene rings of the polystyrene in immobilizing $Sc(OTf)_3$ was demonstrated by control experiments using polybutadiene or polyethylene instead of polystyrene. While 43% of $Sc(OTf)_3$ [100%=the amount of $Sc(OTf)_3$ immobilized by polystyrene] was bound using polybutadiene, no $Sc(OTf)_3$ was observed in the microcapsules prepared using polyethylene. These results demonstrate that the interaction between $Sc(OTf)_3$ and the benzene rings of polystyrene is a key to immobilizing $Sc(OTf)_3$. Steric factors (physical envelopment) would also contribute to the remarkable immobilizing ability of polystyrene compared to poor immobilization of polybutadiene and polyethylene.

MC $Sc(OTf)_3$ was used in several fundamental and important Lewis acid catalyzed carbon–carbon bond-forming reactions. All the reactions were carried out on a 0.5 mmol scale in acetonitrile [34] using MC $Sc(OTf)_3$ containing ca. 0.120 g $Sc(OTf)_3$. The reactions were carried out in both batch (using normal vessels) and flow systems (using circulating columns). It was found that MC $Sc(OTf)_3$ effectively activated aldimines. Imino aldol (Sheme 16), aza Diels–Alder (Scheme 17), cyanation (Scheme 18), and allylation (Scheme 19) reactions of aldimines proceeded smoothly using MC $Sc(OTf)_3$ to afford, respectively, the synthetically useful β-amino ester, tetrahydroquinoline, α-aminonitrile, and homoallylic amine derivatives in high yields.
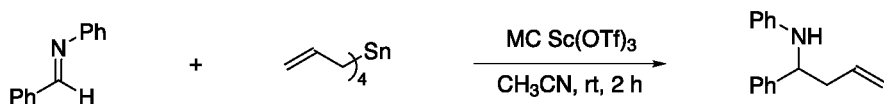
Although it is well known that most Lewis acids are trapped and sometimes decomposed by basic aldimines, MC $Sc(OTf)_3$ worked well in all cases. One of the most remarkable and exciting points is that the activating ability of

Scheme 17. Aza-Diels–Alder reaction (flow system)
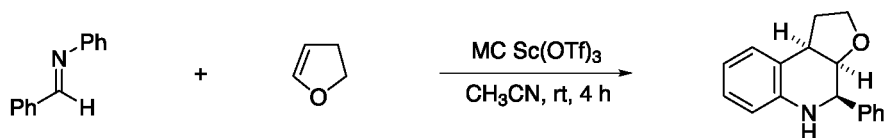
Use	Yield/%
1	80
2	78
3	78

Scheme 18. Cyanation reaction (flow system)

Use	Yield/%
1	77
2	77
3	76

Scheme 19. Allylation reaction of imine (flow system)

Use	Yield/%
1	85
2	87
3	83

MC Sc(OTf)$_3$ for aldimines was revealed to be superior to monomeric Sc(OTf)$_3$ by preliminary kinetic studies (Fig. 3) [35].

The polymer catalyst was recovered quantitatively by simple filtration and could be reused. The activity of the recovered catalyst did not decrease even after seven uses (Scheme 16). MC Sc(OTf)$_3$ could also be successfully used in three-
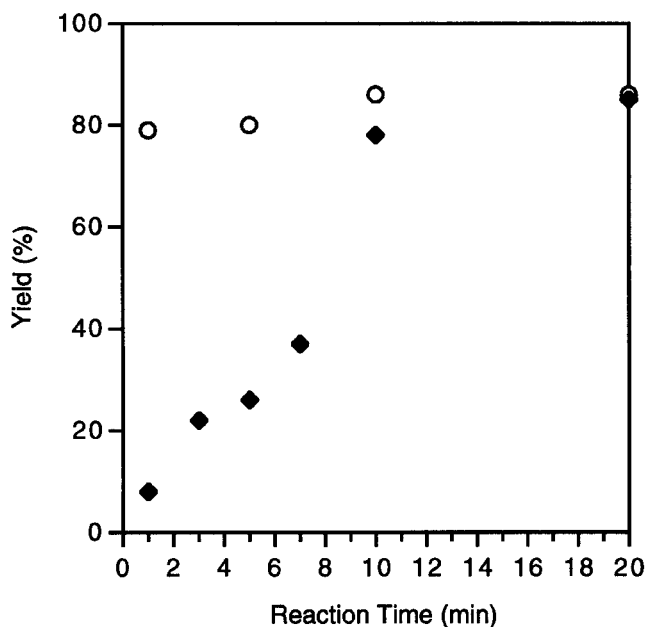
Fig. 3. Comparison of MC Sc(OTf)$_3$ (O) and Sc(OTf)$_3$ (◆) in the reaction of *N*-benzylideneaniline with (*Z*)-1-phenyl-1-trimethylsiloxypropene. The reaction was carried out using *N*-benzylideneaniline (0.5 mmol), (*Z*)-1-phenyl-1-trimethylsiloxypropene (0.60 mmol), and MC Sc(OTf)$_3$ [1.167 g, containing Sc(OTf)$_3$ 0.120 g] or Sc(OTf)$_3$ (0.120 g) in CH$_3$CN (5 ml) at rt
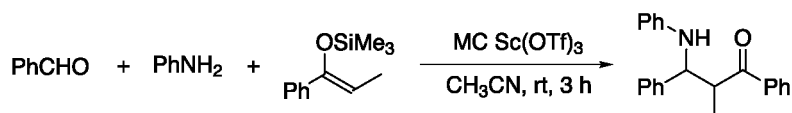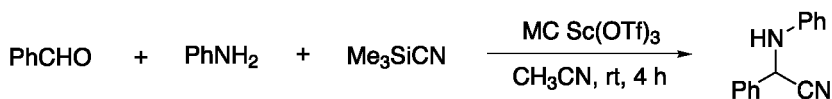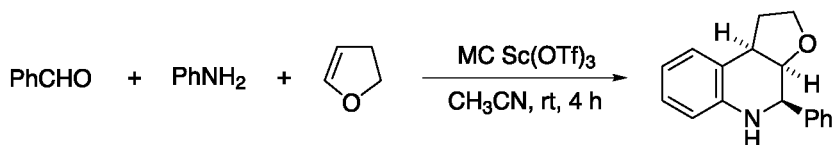

Use	Yield/%
1	90
2	96
3	93

Scheme 20. Mannich-type reaction (flow system)

component reactions such as Mannich-type (Scheme 20), Strecker (Scheme 21), and quinoline-forming reactions (Scheme 22). These reactions are known to be useful for the synthesis of biologically interesting compound libraries [36].

It was also found that MC Sc(OTf)$_3$ was effective for the activation of carbonyl compounds. The polymer scandium catalysts such as Nafion-Sc, polyallylscan-

PhCHO + PhNH₂ + Me₃SiCN $\xrightarrow[\text{CH}_3\text{CN, rt, 4 h}]{\text{MC Sc(OTf)}_3}$

Use	Yield/%
1	70
2	71
3	75

Scheme 21. Strecker reaction (flow system)

PhCHO + PhNH₂ + [furan structure] $\xrightarrow[\text{CH}_3\text{CN, rt, 4 h}]{\text{MC Sc(OTf)}_3}$

Use	Yield/%
1	68
2	69
3	69

Scheme 22. Quinoline synthesis (flow system)

PhCHO + [ketene silyl acetal OSiMe₃/OMe] $\xrightarrow[\text{CH}_3\text{CN, rt, 6 h}]{\text{MC Sc(OTf)}_3}$
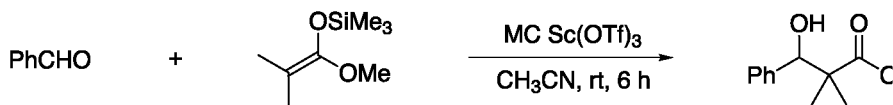
Use	Yield/%
1	92
2	97
3	95

Scheme 23. Aldol reaction (batch system)

dium triflyamide ditriflate (PA-Sc-TAD) were found to have only a low ability to activate aldehydes, as mentioned previously. On the other hand, MC Sc(OTf)₃ efficiently activated aldehydes, and aldol (Scheme 23), cyanation (Scheme 24) and allylation (Scheme 25) reactions of aldehydes proceeded smoothly to give the corresponding aldol, cyanohydrin, and homoallylic alcohol derivatives in high yields.

Use	Yield/%
1	79
2	78
3	74

Scheme 24. Cyanation reaction of an aldehyde (batch system)
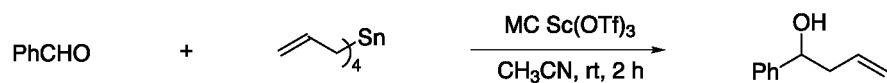
Use [a]	Yield/%
1	92
2	91
3	90

Scheme 25. Allylation reaction of an aldehyde (batch system)
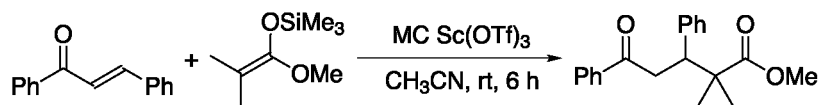
Use	Yield/%
1	92
2	97
3	95

Scheme 26. Michael reaction (batch system)

Michael reaction of an α,β-unsaturated ketone with a silyl enol ether (Scheme 26) and a Diels–Alder reaction of an oxazolidinone derivative with cyclopentadiene (Scheme 27) also worked well using MC Sc(OTf)$_3$. Moreover, a Friedel–Crafts acylation proceeded smoothly to produce an aromatic ketone in a good yield (Scheme 28). Friedel–Crafts alkylation and acylation reactions are fundamental and important processes in organic synthesis as well as in indus-
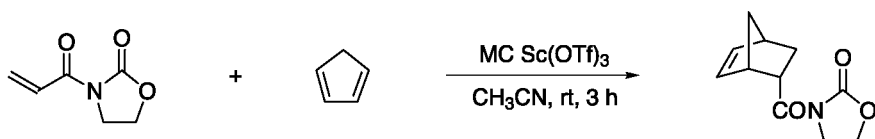
Use	Yield/%
1	77
2	79
3	80

Scheme 27. Diels–Alder reaction (batch system)
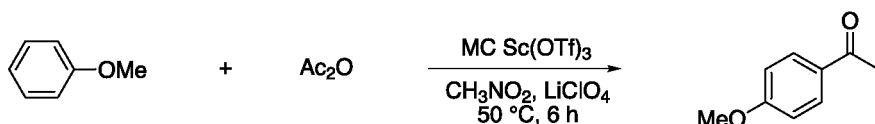
Use	Yield/%
1	76
2	76
3	81

Scheme 28. Friedel–Crafts acylation (batch system)

trial chemistry [37]. While the alkylation reaction proceeds in the presence of a catalytic amount of a Lewis acid, the acylation reaction generally requires more than a stoichiometric amount of a Lewis acid, usually aluminum chloride ($AlCl_3$), due to consumption of the Lewis acid by coordination to the aromatic ketone products. It should be noted that MC $Sc(OTf)_3$ has high activity in the Friedel–Crafts acylation and can be recovered easily by simple filtration and re-used without loss of activity.

Similarly, microencapsulated ytterbium triflate (MC $Yb(OTf)_3$) has been pre-pared [38]. MC $Yb(OTf)_3$ was found to be effective in the aza-Diels–Alder reac-tion using ethyl vinyl ether as a dienophile (Scheme 29). In the presence of MC $Yb(OTf)_3$, N-benzylideneaniline reacted with ethyl vinyl ether to afford the corresponding tetrahydroquinoline derivative in a good yield. MC $Yb(OTf)_3$ could also be recovered quantitatively and could be reused. The yield of the 2nd and 3rd runs were comparable to that of the 1st run. In a similar reaction using $Sc(OTf)_3$ or MC $Sc(OTf)_3$ as a catalyst, ethyl vinyl ether polymerized rapidly and no desired adduct was obtained.
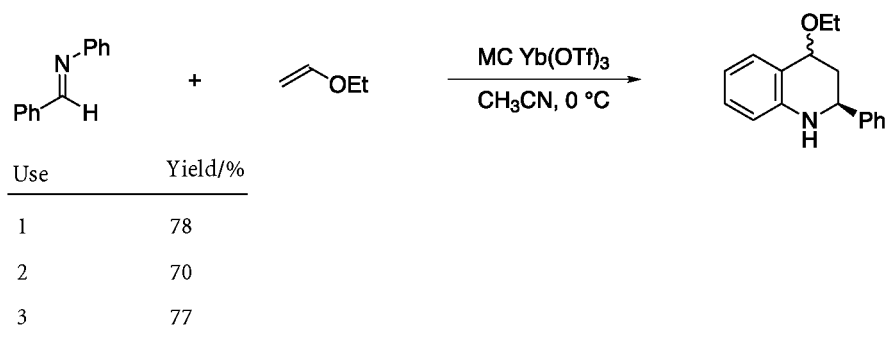
Scheme 29. Aza-Diels–Alder reaction using Yb(Otf)$_3$ (batch system)

Thus, a microencapsulation technique has been shown to be quite effective for binding catalysts to polymers. Utilizing this technique, unprecedented polymer-supported, microencapsulated rare earth Lewis acids have been prepared. The catalysts thus prepared have been successfully used in many useful carbon–carbon bond-forming reactions. In all cases, the catalysts were recovered quantitatively by simple filtration and reused without loss of activity. This new technique for binding nonpolymer compounds to polymers will be applicable to the preparation of many other polymer-supported catalysts and reagents.

5
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10. $ScCl_3 \cdot 6H_2O$ (519 mg, 2.0 mmol) and Nafion (5 g, 1.2 meq/g) were combined in acetonitrile (10 ml) under reflux for 40 h. After cooling to rt, the polymer was filtered, washed with acetonitrile (20 ml×3), and then dried under reduced pressure for 24 h. A trial to prepare Nafion-Sc from Sc_2O_3 and Nafion failed (only 0.1% Sc was included in the polymer (ICP analysis))

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16. Nafion-Sc (2 g) and sea sand (2 g, 15–20 mesh) were combined and the mixture was packed in a 6-mm glass tube. A carbonyl compound (0.5 mmol) and tetreallyltin (0.5 mmol) were dissolved in acetonitrile (4 ml) and passed through the column using a peristaltic pump (EYELA, MP-3)

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32. Judging from the recovered $Sc(OTf)_3$ (0.080 g), 0.120 g of $Sc(OTf)_3$ was microencapsulated according to this procedure. The weight of the capsules was 1.167 g which contained acetonitrile. MC $Sc(OTf)_3$ thus prepared can be stored at rt for more than a few months
33. IR (KBr) 3062, 3030 (vCH), 1946, 1873, 1805 (δCH), 1601, 1493 (benzene rings). 1255 ($v_{as}SO_2$), 1029 (v_sSO_2), 756 (vC-S), 696 (vS-O) cm^{-1}. Cf. $Sc(OTf)_3$: 1259 ($v_{as}SO_2$), 1032 (v_sSO_2), 769 (vC-S), 647 (vS-O) cm^{-1}; polystyrene: 3062, 3026 (vCH), 1944, 1873, 1803 (δCH), 1600, 1491 (benzene rings) cm^{-1}
34. Nitromethane was used in Friedel–Crafts acylation (Scheme 28)
35. Although the origin of the high activity of MC $Sc(OTf)_3$ is not clear at this stage, it was reported that aldimine–Lewis acid complexes were stabilized by using a polymer-supported Lewis acid. Cf. [24]
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